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Chiral Imidazoline Nitrones for Cycloaddition Reactions

by

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Thesis submitted to the Open University

for the Degree of Doctor of Philosophy

December 1999

For my brother and my parents

Declaration

I declare that the work presented in this thesis is the result of my own investigations, and where the work of others is cited, it is fully acknowledged. The material embodied in the thesis has not been submitted, nor is currently being submitted for any other degree.

.....

Jason N. Martin

.....

Prof. R. C. F. Jones

Supervisor

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I extend my thanks in the first instance to Ray for his supervision and guidance, but especially for his happy-go-lucky approach with the RCFJ-group chequebook when it came to conferences, glassware and chemicals. Secondly, I thank my industrial supervisor Paul Smith and his group at SmithKline Beecham, Harlow. I turned a corner with this work during my time with his group and I thank them all for their help and their tolerance. Grateful thanks go to EPSRC and SB for their generous financial support.

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Abstract

Previous work in this group has demonstrated that azomethine ylide 1,3-dipoles based on the 2-imidazoline chiral template show high regio- and enantioselectivity in their 1,3-dipolar cycloaddition reactions with a range of dipolarophiles. We proposed to synthesise nitron 1,3-dipoles based on this 2-imidazoline template in order to investigate their utility in 1,3-dipolar cycloaddition chemistry.

We have developed the synthesis of chiral 4-phenyl-2-imidazoline nitrones **126a-c** *via* a key hydroxylamino amine dihydrochloride intermediate **140a**, available in four steps (61% overall yield) from commercial 2-chloroacetophenone. Nitrones **126a** & **126b** are generated rapidly and quantitatively from **140a** by treatment with the appropriate triethyl orthoester. 2-Methyl nitron **126b** does not undergo a 1,3-dipolar cycloaddition reaction with common dipolarophiles, suggesting C-2 substitution is not tolerated in the transition state. On the other hand, we have shown 2-H nitron **126a** to react with many mono- and disubstituted alkynes and alkenes. The relative stereochemistry of the cycloadducts formed with **126a** has been assigned by NOESY and X-ray crystallography. In each case, the dipole shows total diastereofacial selectivity in which the incoming dipolarophile is directed to the less hindered face of **126a** by the bulky 4-phenyl group. The isolated cycloadducts are, almost without exception, formed *via* the *exo* transition state.

The cycloadduct of **126a** with dimethyl maleate has been the focus of our efforts towards cleavage of the 2-imidazoline template. It is unreactive towards the conditions developed for template removal in the analogous azomethine ylides, despite many modifications. Cleavage of the isoxazolidine N–O bond followed by spontaneous lactamisation afforded the lactam **271**. Reduction of the lactam carbonyl would afford the

pyrroloimidazole ring system, for which a template removal strategy is in place, but **271** has not to date afforded the desired material under a number of reaction conditions. For example, borane-complexed reagents gave a partially aromatised system in which three chiral centres are lost.

Thus, we have illustrated that these reagents, available from cheap commercial materials, are viable 1,3-dipoles capable of generating multiple chiral centres in a single step with total facial selectivity and have made progress towards the synthesis of chiral pyrrolidines.

Abbreviations

The following symbols and abbreviations are used in this text:

$[\alpha]_{\text{D}}^{20}$	specific rotation (measured with sodium D line, sample at 20°C), in degrees
Å	angstroms
Ac	acetyl
APCI ⁺ MS	atmospheric pressure chemical ionisation mass spectrometry (positive ion mode)
aq.	aqueous
atmos.	atmosphere (pressure)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
bp	boiling point
c. or conc.	concentrated
cat.	catalyst
Cbz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	see DCCI
DCCI	dicyclohexylcarbodiimide
DCM	dichloromethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate

DEM	diethyl maleate
DIBAL	diisobutylaluminium hydride
DMAD	dimethyl acetylenedicarboxylate
DMF	dimethylformamide
DMM	dimethyl maleate
DMSO	dimethylsulfoxide
equivs.	molar equivalents
FMO	Frontier Molecular Orbital
gl.	glacial
h	hours
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HOSu	N-hydroxysuccinimide
HPLC	high performance liquid chromatography
Hz	hertz
inj.	injection
IR	infrared
LUMO	lowest unoccupied molecular orbital
M ⁺	molecular ion
<i>m</i> -CBA	<i>m</i> -chlorobenzoic acid
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid
MHz	megahertz
min	minutes
mmol	millimoles

mol%	percentage by moles
mp	melting point
MS	mass spectrometry
<i>m/z</i>	mass to charge ratio
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy (2-dimensional)
PCC	pyridinium chlorochromate
5% Pd-C	palladium adsorbed on carbon (5% w/w)
Ph-Gly	phenylglycine
PNB	<i>p</i> -nitrobenzyl
psi	pounds per square inch
<i>p</i> -Ts	<i>p</i> -toluenesulfonyl
py	pyridine
Ra-Ni	Raney Nickel catalyst
redn.	reduction
SiO ₂	silica gel
soln.	solution
TBAF	tetrabutylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDMSCl	<i>tert</i> -butyldimethylsilylchloride
TBDPS	<i>tert</i> -butyldiphenylsilyl
^t Bu	<i>tert</i> -butyl

temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane or trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	see <i>p</i> -Ts
TsOH	<i>p</i> -toluenesulfonic acid
TSP-d ₄	3-(trimethylsilyl)-2,2,3,3-tetradeuteropropionic acid sodium salt
v/v	proportions of two components expressed as a ratio of their volumes
w/w	proportions of two components expressed as a ratio of their masses

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Chapter 1

Introduction

1.1 The 1,3-dipolar cycloaddition reaction

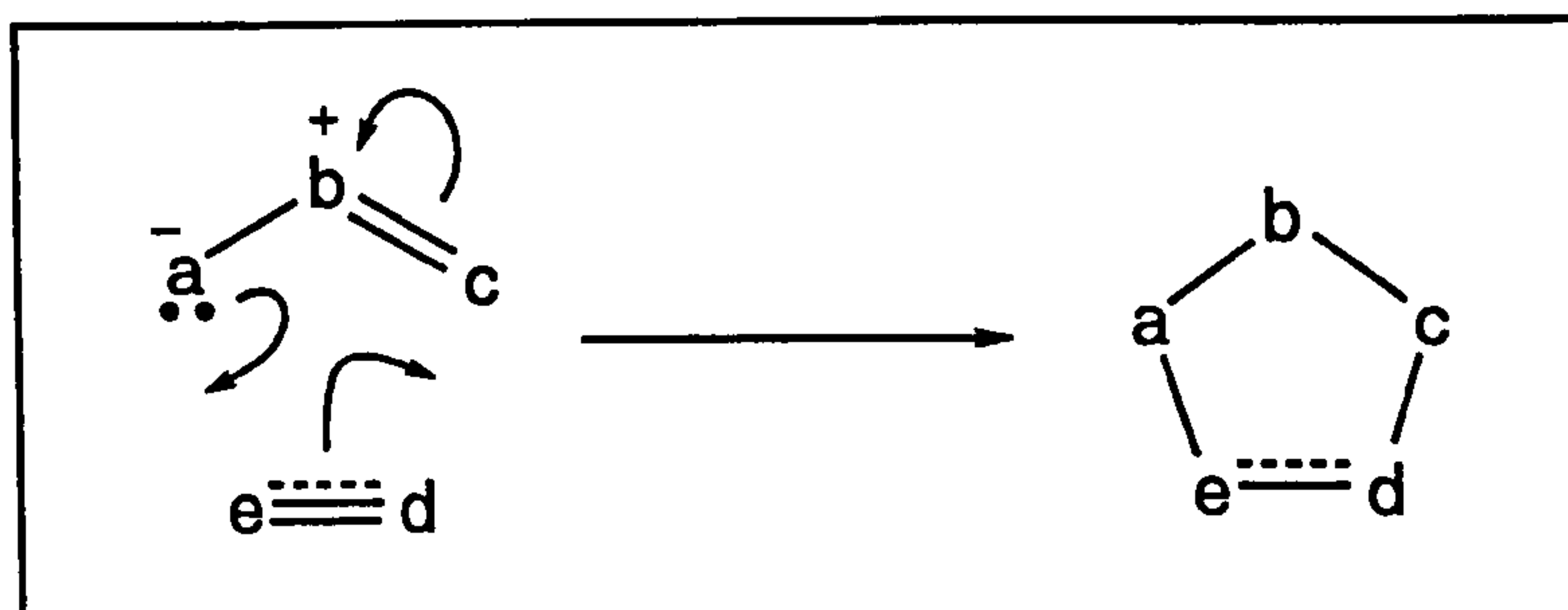


Figure 1 : 1,3-Dipolar cycloaddition.

Our knowledge of 1,3-dipolar cycloaddition reactions goes back to the discovery of diazoacetic ester by Curtius in 1883^{1,2} and the elucidation by Ley of the structure of fulminic acid in 1899 - the first 1,3-dipoles. In 1893 Buchner, a colleague of Curtius, reacted diazoacetic ester with methyl acrylate to produce pyrazolines in the first example of a 1,3-dipolar cycloaddition reaction.³ However, it was not until Huisgen proposed the concept of 1,3-dipolar cycloadditions in 1960 that the full scope of these reactions began to be realised.⁴ The product of the bimolecular reaction between the 1,3-dipole ($+a-b-c^-$) and a multiply-bonded system ($d=e$ or $d\equiv e$), the “dipolarophile”, is a 5-membered ring (Figure 1); judicious choice of 1,3-dipole and dipolarophile allows access to a plethora of possible carbocyclic and heterocyclic ring systems. The large volume of recent literature in this field is testament to the fact that these reactions are not only versatile, but also highly robust.⁵⁻¹⁰ They represent a powerful tool in modern synthetic chemistry, whose limits are still being explored more than a century after their discovery.

1.1.1 The 1,3-dipole

The term 1,3-dipole describes a range of 3-atom systems which can only be represented by ground state zwitterionic resonance structures, one of which has the charges at the terminal atoms (atoms 1 and 3). It was deduced from experimental models⁶ that the allyl-anion type orbitals (four π electrons in three parallel atomic orbitals) are responsible for the cycloaddition reaction. However, in contrast with the nucleophilic termini of the allyl anion, the termini of the 1,3-dipole (a “heteroallyl anion”) are both electrophilic and nucleophilic (Figure 2a).

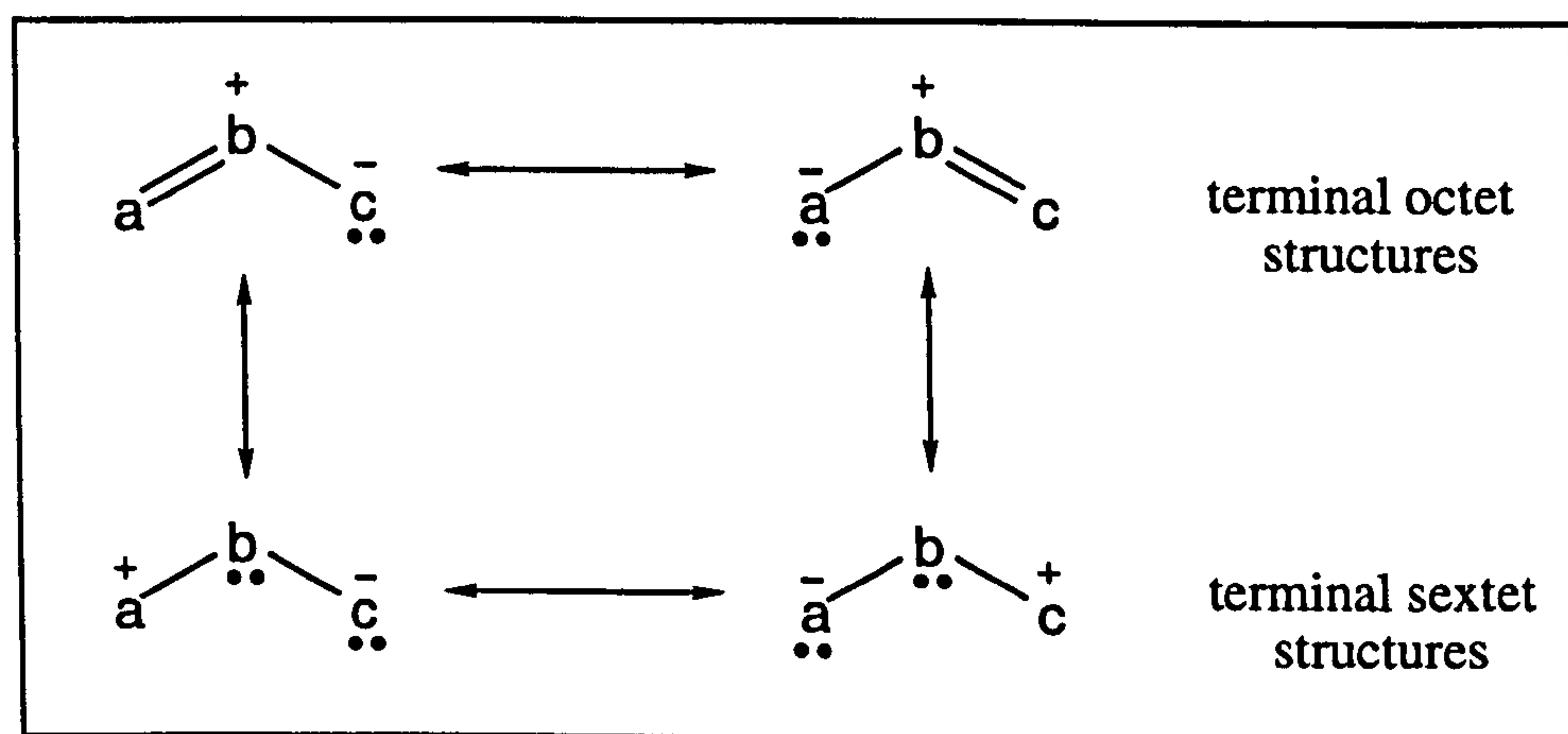


Figure 2a : Resonance structures of allyl-anion type 1,3-dipoles.

A second, smaller class of 1,3-dipoles, the “propargyl-allenyl” type, is provided by incorporating an additional π -bond such that one resonance form contains a triple bond (Figure 2b). These 1,3-dipoles are therefore linear, in contrast to the bent allyl-anion type 1,3-dipoles. Occasionally, the two classes are shown as hypervalent resonance forms (Figure 2c).

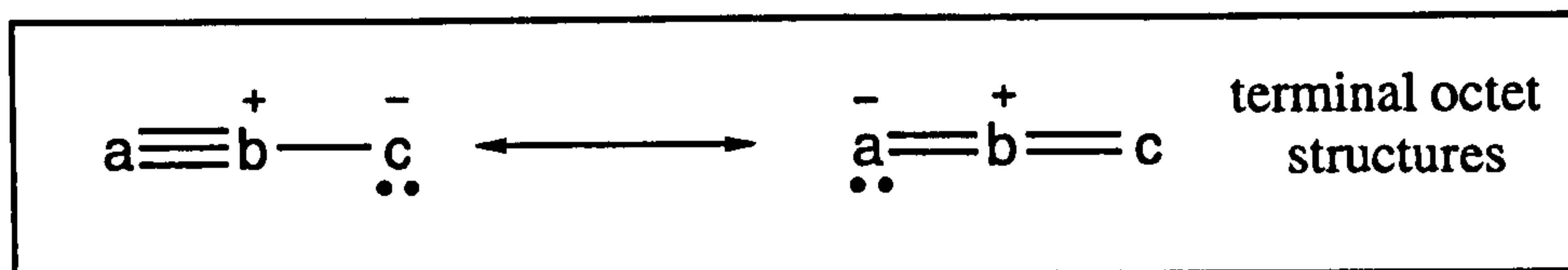


Figure 2b : Propargyl-allenyl type 1,3-dipoles.

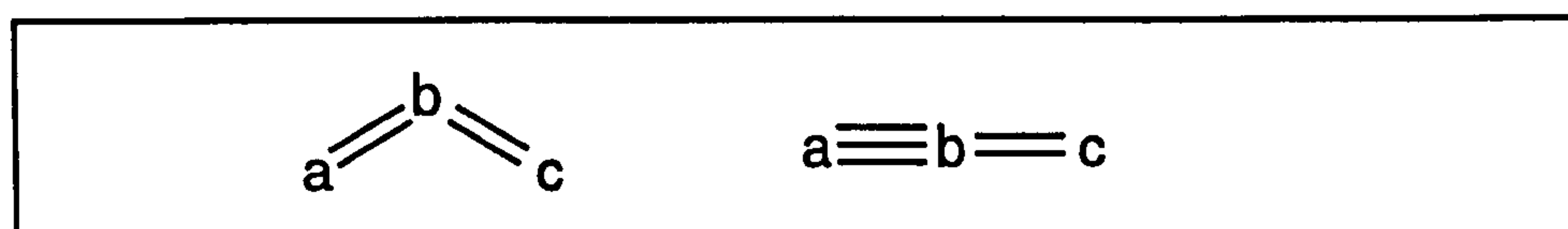


Figure 2c : Hypervalent representations.

Restricting the three atoms of the 1,3-dipole to C, N and O (with a central heteroatom), Huisgen has classified the eighteen possibilities; six propargyl-allenyl and twelve allyl-anion type (Table 1).¹¹ Representatives of almost all classes have been shown to take part in 1,3-dipolar cycloaddition reactions, although those most commonly used are the nitrones, nitrile oxides and azomethine ylides, followed by the azomethine imines, azides and diazoalkanes. Many of these 1,3-dipoles have been isolated and characterised, but it has often been found to be advantageous to generate the dipole *in situ* for subsequent reaction.

A : Allyl-anion type 1,3-dipoles

$\begin{array}{c} \diagup \\ \text{C}=\text{N}^+-\text{C}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{C}^- - \text{N}^+=\text{C} \diagdown \\ \\ \text{:} \end{array}$	Azomethine ylides
$\begin{array}{c} \diagup \\ \text{C}=\text{N}^+-\text{N}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{C}^- - \text{N}^+=\text{N} \diagdown \\ \\ \text{:} \end{array}$	Azomethine imines
$\begin{array}{c} \diagup \\ \text{C}=\text{N}^+-\text{O}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{C}^- - \text{N}^+=\text{O} \diagdown \\ \\ \text{:} \end{array}$	Nitrones
$\begin{array}{c} \diagup \\ \text{N}=\text{N}^+-\text{N}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{N}^- - \text{N}^+=\text{N} \diagdown \\ \\ \text{:} \end{array}$	Azimes
$\begin{array}{c} \diagup \\ \text{N}=\text{N}^+-\text{O}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{N}^- - \text{N}^+=\text{O} \diagdown \\ \\ \text{:} \end{array}$	Azoxy compounds
$\begin{array}{c} \diagup \\ \text{O}=\text{N}^+-\text{O}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{O}^- - \text{N}^+=\text{O} \diagdown \\ \\ \text{:} \end{array}$	Nitro compounds
$\begin{array}{c} \diagup \\ \text{C}=\text{O}^+-\text{C}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{C}^- - \text{O}^+=\text{C} \diagdown \\ \\ \text{:} \end{array}$	Carbonyl ylides
$\begin{array}{c} \diagup \\ \text{C}=\text{O}^+-\text{N}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{C}^- - \text{O}^+=\text{N} \diagdown \\ \\ \text{:} \end{array}$	Carbonyl imines
$\begin{array}{c} \diagup \\ \text{C}=\text{O}^+-\text{O}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{C}^- - \text{O}^+=\text{O} \diagdown \\ \\ \text{:} \end{array}$	Carbonyl oxides
$\begin{array}{c} \diagup \\ \text{N}=\text{O}^+-\text{N}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{N}^- - \text{O}^+=\text{N} \diagdown \\ \\ \text{:} \end{array}$	Nitrosimines
$\begin{array}{c} \diagup \\ \text{N}=\text{O}^+-\text{O}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{N}^- - \text{O}^+=\text{O} \diagdown \\ \\ \text{:} \end{array}$	Nitrosoxides
$\begin{array}{c} \diagup \\ \text{O}=\text{O}^+-\text{O}^- \diagdown \\ \\ \text{:} \end{array}$	\longleftrightarrow	$\begin{array}{c} \diagup \\ \text{O}^- - \text{O}^+=\text{O} \diagdown \\ \\ \text{:} \end{array}$	Ozone

Table 1 : Heteroatom-based 1,3-dipoles.¹¹

B : Propargyl-allenyl type 1,3-dipoles

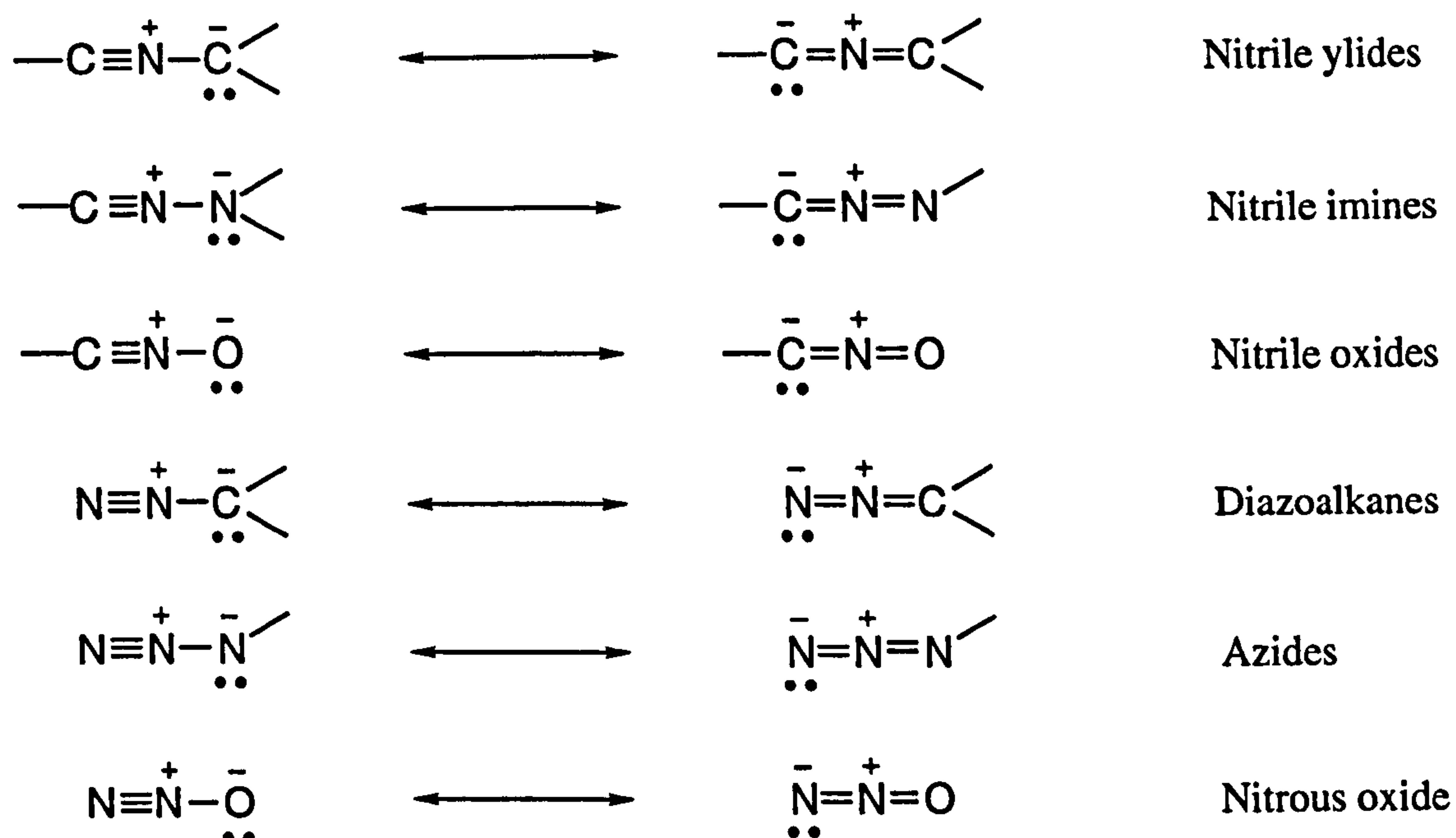


Table 1 (continued) : Heteroatom-based 1,3-dipoles.¹¹

1.1.2 The dipolarophile

A vast number of multiply-bonded structures has been used as dipolarophiles in 1,3-dipolar cycloaddition reactions, though the most common and ultimately most useful are alkenes. Other contenders in terms of popularity include alkynes, isocyanates, imines, carbonyls, thiocarbonyls and azo-compounds. The nature of the dipolarophile has a profound effect on the cycloaddition reaction, not only in terms of its reactivity but also its shape, size and propensity towards non-covalent interactions with the 1,3-dipole.

1.1.3 The cycloaddition mechanism

In 1960, Huisgen proposed the concerted electrocyclic process of 1,3-dipolar cycloaddition which has now won universal acceptance with little need for refinement. A year later, Doering and Roth described these reactions as "no mechanism" processes - highlighting the fact that the theory explained much but accepted many odd results.¹² By 1968, the weight of experimental evidence allowed Huisgen to say that their view showed "pessimism...which seems no longer justified".¹³

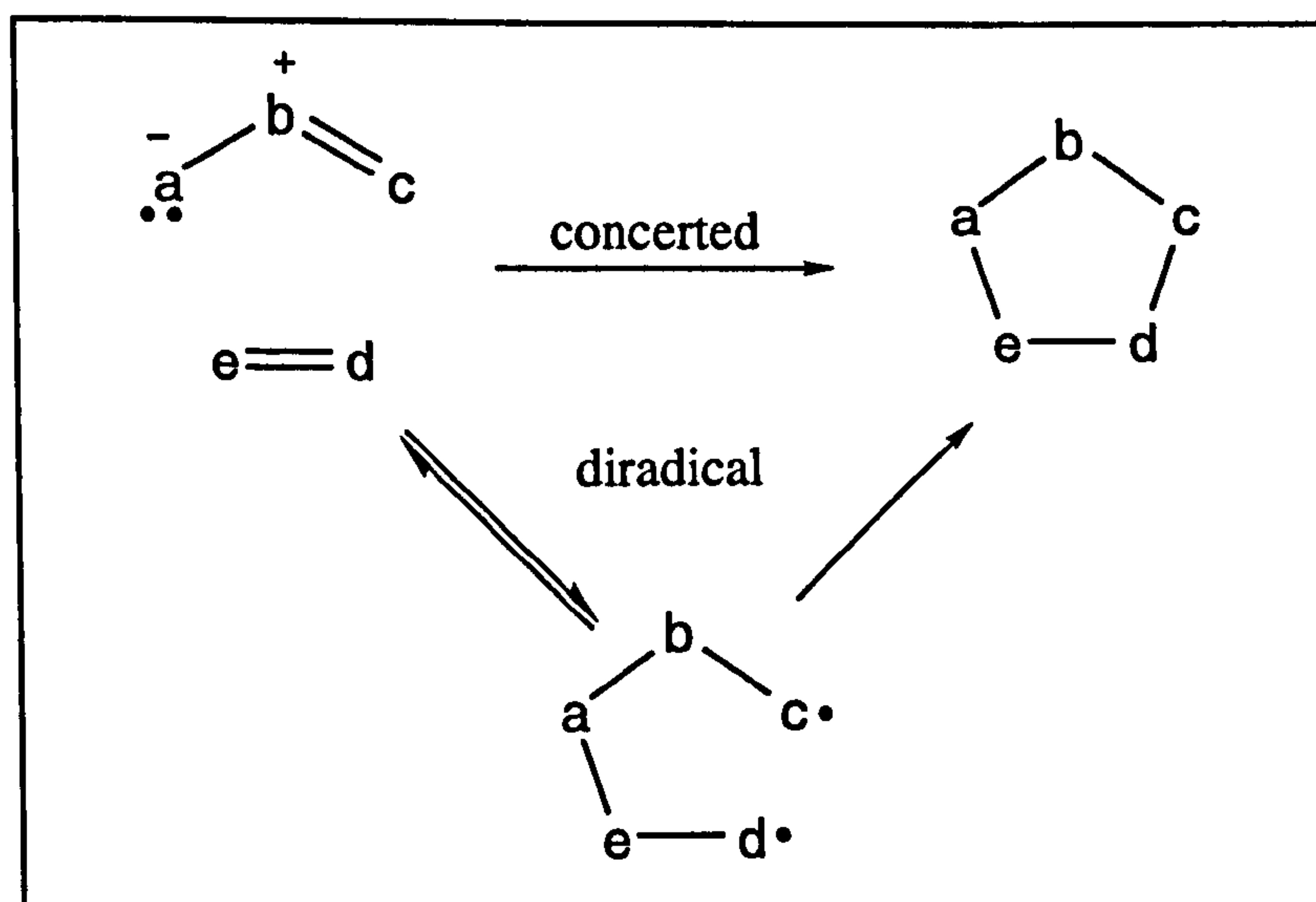


Figure 3 : Concerted and di-radical mechanism of 1,3-dipolar cycloaddition.

In 1968, an alternative to the concerted, single-step cycloaddition mechanism was proposed by Firestone involving a two-step reaction which proceeds *via* a di-radical intermediate (Figure 3).¹⁴⁻¹⁶ Huisgen championed the concerted mechanism, citing the abundant examples of stereospecific addition in the literature as the essential supporting proof of this mechanism. He argued that for the general rule of high stereospecificity of these reactions to be upheld by the di-radical mechanism, the energy barrier to rotation around the

single bond d–e of the di-radical, once formed, must be less than the barrier to the cyclisation that would yield the cycloadduct. He calculated that the energy of rotation of the potential diradical intermediates for a number of known 1,3-dipolar cycloaddition reactions would need to be zero, and so demonstrated that the energy profile cannot contain the di-radical as an intermediate.¹¹ The debate between Huisgen and Firestone (later chronicled by Houk *et al.*)¹⁷ was long and intense, and included back-to-back papers in the *Journal of Organic Chemistry*.^{13,14} The contest looked to have been decided when Houk and Firestone were able to show that a nitrile oxide 1,3-dipole reacts with *cis*- or *trans*- deuterioethylenes in a cycloaddition reaction that was more than 98% stereospecific.¹⁸ They concluded that the reactions were concerted processes with no intermediates, in accordance with the predicted products from Huisgen's proposed mechanism. Somewhat ironically, Huisgen then reported the first well-documented stepwise 1,3-dipolar cycloaddition involving an intermediate, but stressed that this only served to further support the concerted mechanism for the majority of cycloaddition reactions since they lack the stereochemical scrambling characteristic of the stepwise process.^{19,20}

The high regio- and stereoselectivity of these reactions is widely interpreted as an indication that the addition takes place *via* a highly ordered aromatic transition state, a feature shared with the Diels-Alder reaction. This interpretation is supported by a number of experimentally-determined parameters for 1,3-dipolar cycloaddition reactions :⁶

- the reaction rate is largely independent of solvent polarity,
- the entropy of activation tends to be large and negative,
- the enthalpy of activation tends to be modest.

This high degree of order during the bond-forming process means that chiral information in the dipole or dipolarophile may be used to enforce a particular orientation of

the two components in the transition state. Thus, the desired chirality in the cycloadduct may be produced by judicious selection of the chiral component of the cycloaddition. First, however, we must consider the source and nature of the possible transition state geometries.

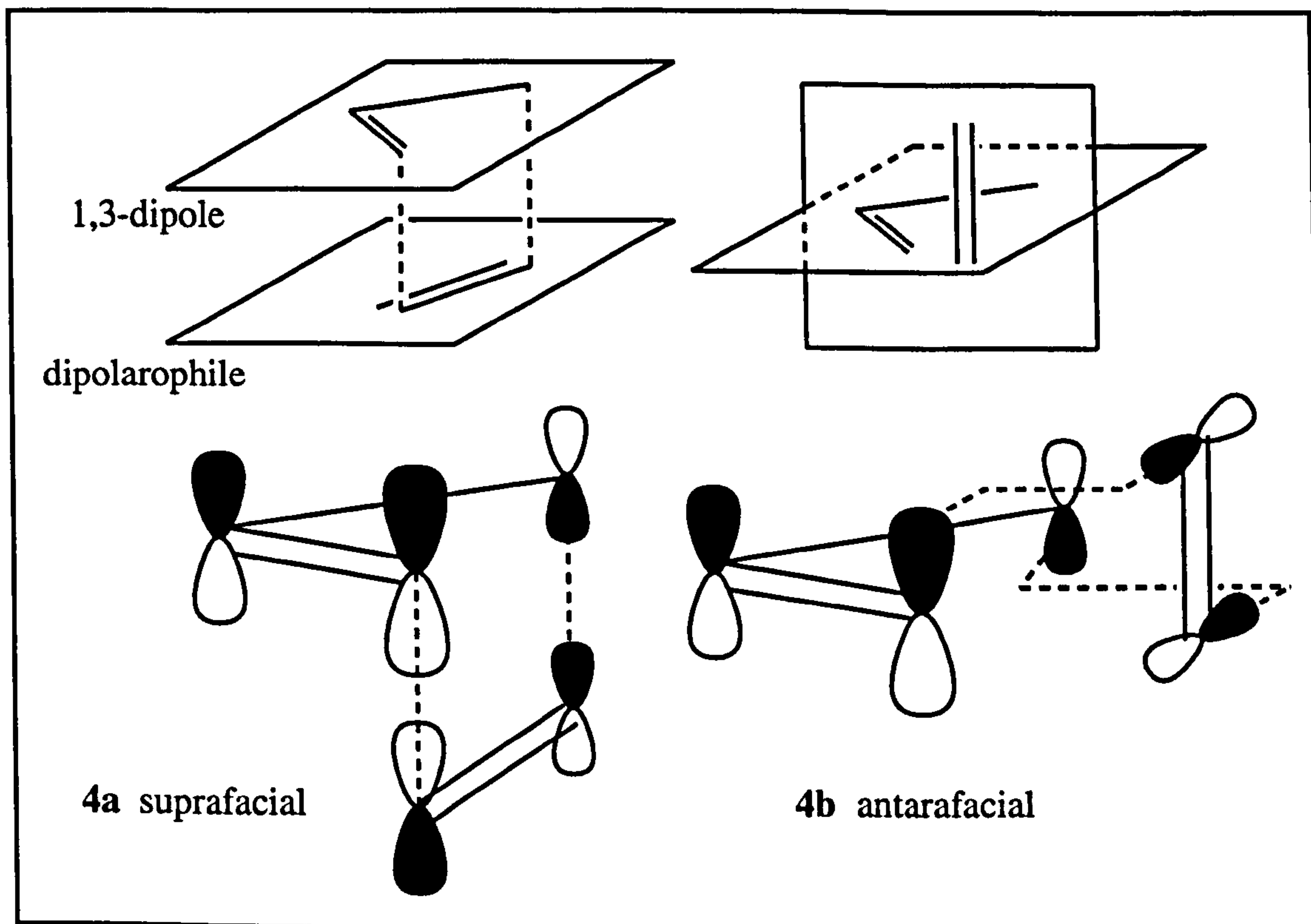


Figure 4 : Possible orientations of the dipole and dipolarophile in a 1,3-dipolar cycloaddition reaction.

It is generally accepted that in the 1,3-dipolar cycloaddition reaction the 1,3-dipole and the dipolarophile will prefer to approach one another as 'stacked planes'.²¹ A reaction in which the new bonds form on the *same* surface of a particular reactant is described as *suprafacial* in that component. Figure 4a shows the orientation of an allyl-anion type 1,3-dipole and an alkene dipolarophile in a cycloaddition which is suprafacial in both components. As the reactants approach one another along the axis of bond formation (shown by dotted lines), it is clear that this transition state facilitates overlap of the relevant molecular

orbitals. We would expect the same high degree of orbital overlap were the dipolarophile to approach the top face of the 1,3-dipole rather than from underneath as shown.

Alternatively, if one bond is formed on one surface of a reactant and one bond is formed on the other surface, then the reaction is described as *antarafacial* in that component (Figure 4b). This diagram shows that we can consider the two planar components of the cycloaddition now approaching at right angles to each other. Figure 4b demonstrates that reactions involving one antarafacial component have much more exacting spatial requirements, and effective orbital overlap is much more difficult to achieve. Such reactions are rare and it is clear that optimum overlap of the molecular orbitals of the two components in a 1,3-dipolar cycloaddition reaction, and so formation of the major product, most often occurs *via* the suprafacial orientation.

Even with this much decided, there are still a number of different ways in which the orientation of approach of the 1,3-dipole to the dipolarophile will determine the eventual regio- and stereochemistry of the cycloadduct. Firstly, the planar 1,3-dipole may be approached from above or below, each face giving rise to different stereochemistry in the adduct. This fact has not gone unnoticed - many reagents have been developed that are facially differentiated in order to direct incoming dipolarophiles.

When substituents are added to the dipolarophile it becomes apparent that further possibilities present themselves whilst maintaining the suprafacial arrangement of the two reactants. Firstly, the dipolarophile may approach with the substituent directly beneath the 1,3-dipole during bond formation - this is the *endo* transition state (Figure 5). Such a transition state may become the energetically more favourable pathway by finding some extra stabilisation from a non-covalent interaction between the dipole and the substituent Z. An example is the stacking of π -systems on dipole and dipolarophile. Alternatively, where, for

instance, Z is a bulky group, steric factors may force the dipolarophile to approach with the substituent pointing away from the dipole; in this case bonding will occur *via* the *exo* transition state.

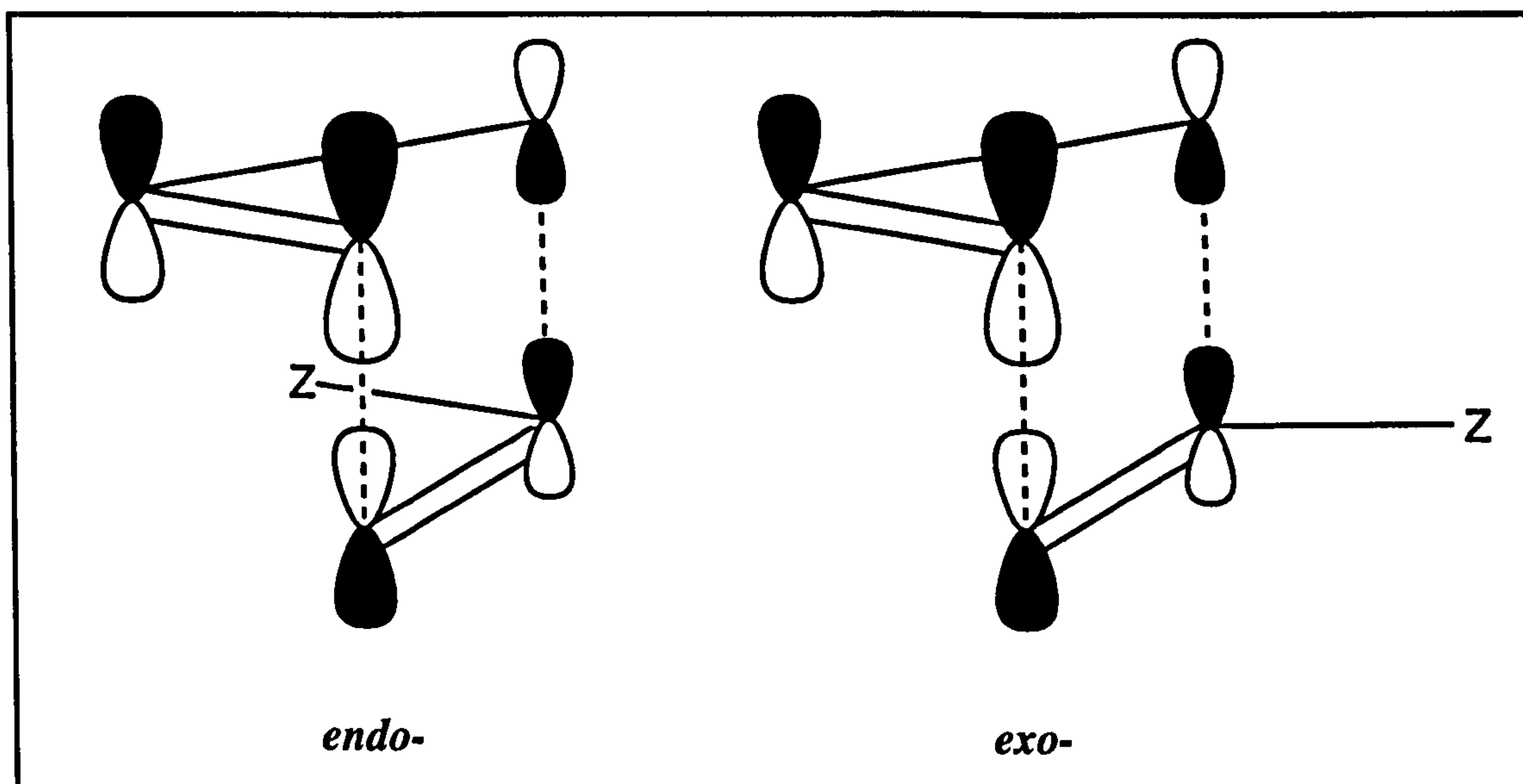


Figure 5 : 1,3-Dipolar cycloaddition transition states.

1.1.4 Frontier Molecular Orbital (FMO) theory

Whilst the concerted nature of the 1,3-dipolar cycloaddition reaction was being debated, the factors that governed the regiochemistry still remained a mystery. In 1972, Fukui demonstrated that the regiochemistry can be explained most reliably by Frontier Molecular Orbital (FMO) theory, for which he shared the 1981 Nobel Prize for Chemistry with Hoffmann.²² He proposed that the cycloadditions take place in the direction of maximum overlap of the frontier molecular orbitals of the 1,3-dipole and dipolarophile, in other words, the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of each component. By the Woodward-Hoffmann theory of

conservation of orbital symmetry,²³ it can be seen that the interaction of the HOMO of one component with the LUMO of the other is symmetry allowed and would represent the strongest bond-making interaction. Fukui reasoned that the optimum orbital overlap occurs between orbitals that are separated by the smallest energy gap, and that the smaller the gap, the faster the rate of reaction. If the relative energies of these FMOs are known it should therefore be possible to predict the dominant FMO interaction - with this information we can often then directly predict the preferred regiochemistry of the reaction.

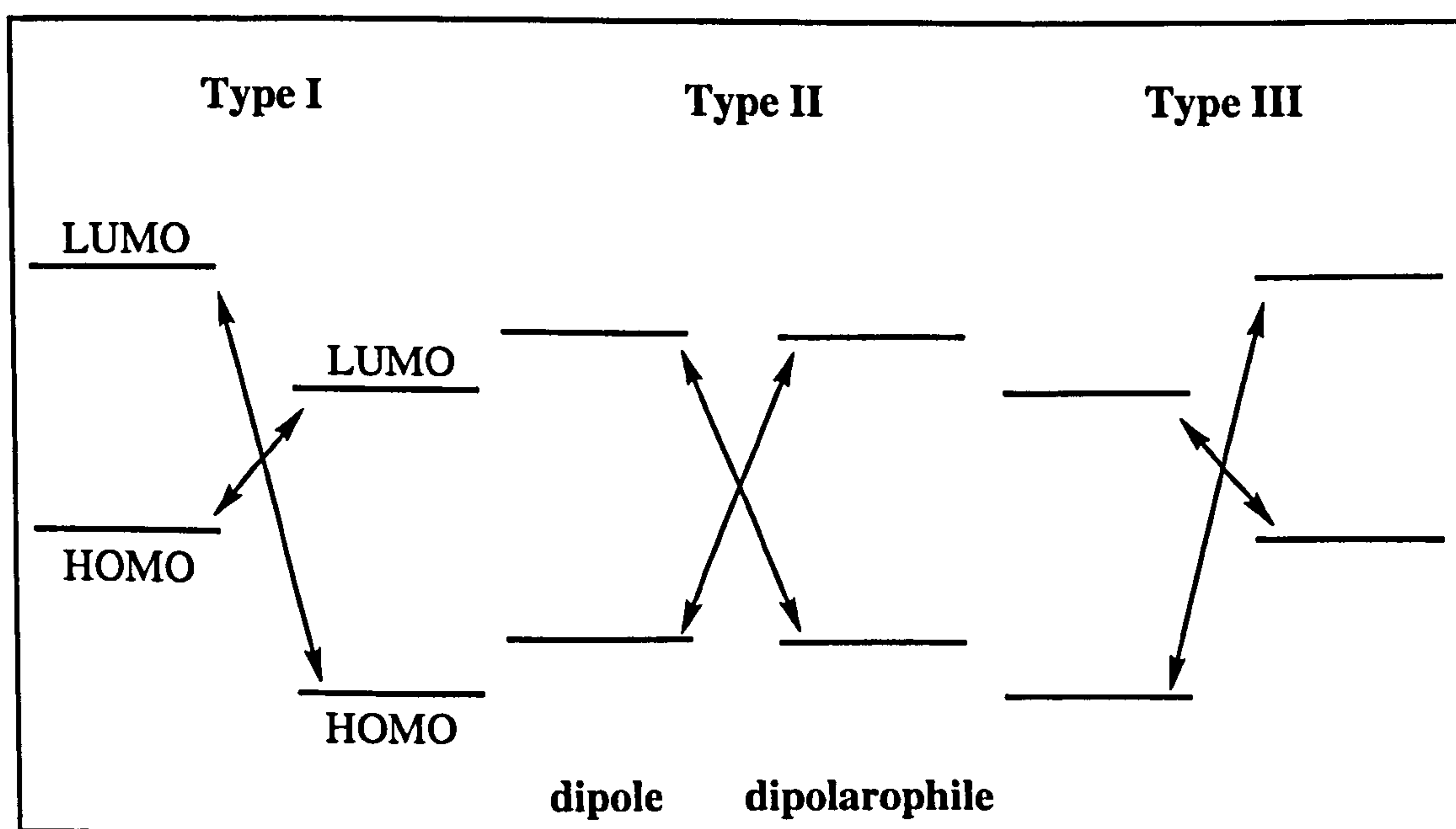


Figure 6 : Sustmann model of FMO theory.

Sustmann classified the possible modes of interaction of frontier molecular orbitals in dipolar cycloadditions according to their relative energies, recognising three different situations (Figure 6).²⁴ When the HOMO of the 1,3-dipole and the LUMO of the dipolarophile have the smallest energy gap, then the cycloaddition is classed as the Type I case by Sustmann notation. We shall henceforth conform to the recognised convention and refer to such a reaction as HOMO-controlled. Conversely, should the LUMO of the dipole

and the HOMO of the dipolarophile have the smaller energy gap, then this is the Type III case, a reaction exhibiting LUMO-control. Obviously, these two extremes will be bisected by a third situation, in which neither interaction is favoured in frontier orbital terms. This is referred to as the Type II case.

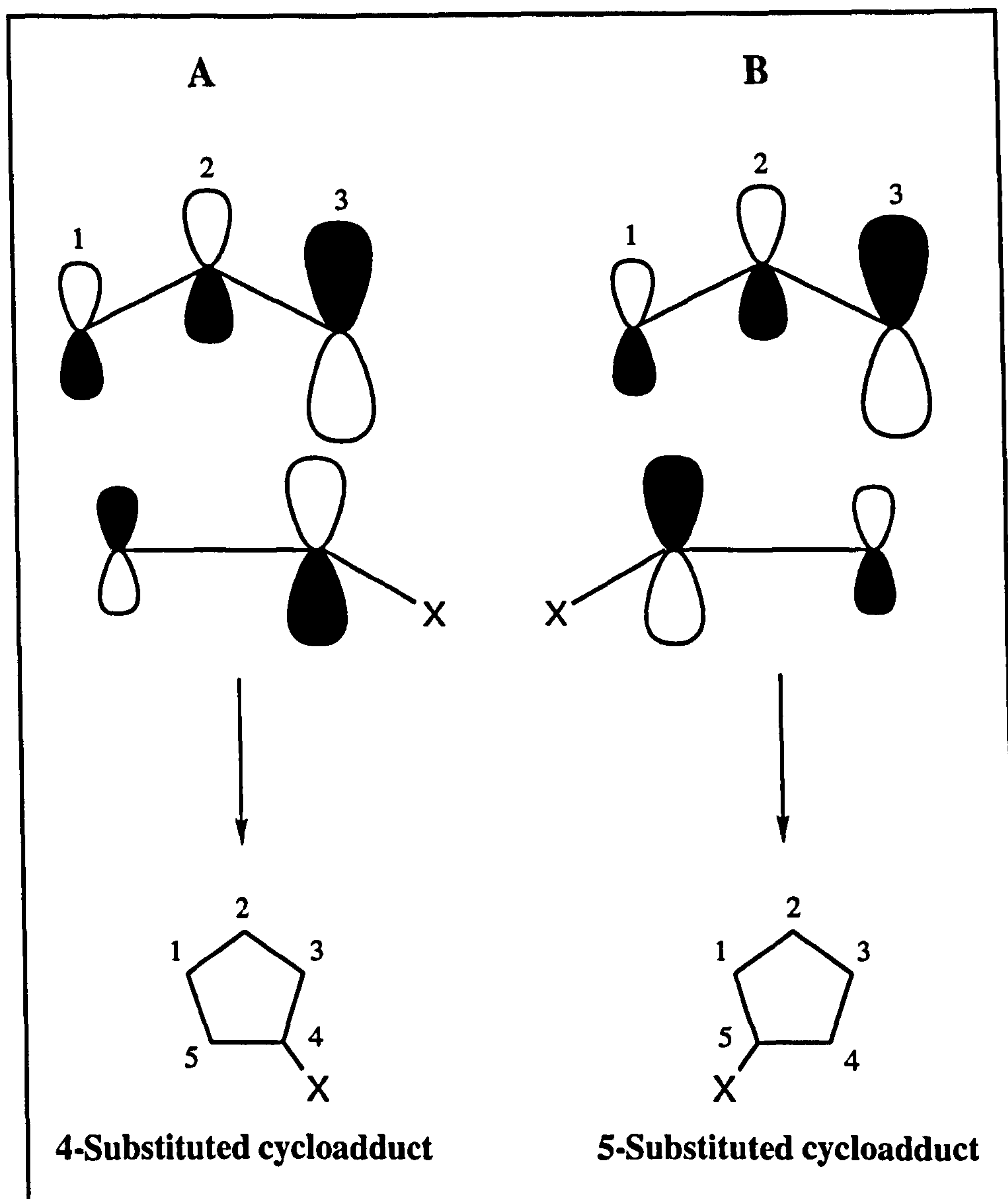


Figure 7 : FMO theory and the regiochemistry of 1,3-dipolar cycloaddition reactions.

In the case of concerted cycloadditions, the preferred regiochemistry depends upon the relative sizes of the orbital coefficients at the reacting termini of the dipole and dipolarophile. Figure 7 shows the orbital coefficients for a cycloaddition in which the

dominant interaction is the dipole HOMO - dipolarophile LUMO, in other words HOMO-control. Here, the lobes have been drawn to represent the sign of the wave function by their shading and the magnitude of the coefficient on that atom by their size. There are two regiochemically different products that arise as a result of the different orientations of the alkene during bond formation. The largest orbital coefficient of the 1,3-dipole is at atom 3 and the smallest coefficient at atom 1, with the dipolarophile orbital coefficient being largest adjacent to the substituent X. Case A in Figure 7 represents the maximum overlap of the molecular orbitals, as in this case the orbital coefficients are matched - large with large, and small with small. We would expect the 4-substituted cycloadduct to be the major product from this reaction. In case B, the orbital coefficients are not matched, and we would predict that the 5-substituted cycloadduct will, as a result, be a minor product.

Both the energy of the frontier molecular orbitals of alkenes and the orbital coefficients at each end of the double bond are affected by the nature of their substituents. Electron-withdrawing groups decrease both HOMO and LUMO energies, especially the LUMO, and in both FMOs the largest coefficient is at the unsubstituted end of the alkene. Conversely, the energy of both FMOs is increased by electron-donating groups, with the largest effect on the HOMO. In this case, the largest orbital coefficient is at the unsubstituted end of the HOMO but at the substituted end of the LUMO. In alkenes containing a conjugating group, the energy of the HOMO is raised but the LUMO is lowered, and the orbital coefficient is largest at the unsubstituted end for both MOs.²⁵

Typical relative energies of the frontier orbitals for the three classes of alkene dipolarophile are shown in Figure 8. Electron-donating groups are represented by the substituent X, and include alkenes such as vinyl ethers. Conjugating groups are represented by C, and electron-withdrawing groups by Z: such alkenes include styrenes and acrylate

esters respectively. Thus, as the rate of the cycloaddition depends on the size of the HOMO-LUMO energy gap, we can imagine that for a chosen dipole, the rate of reaction will be different in its cycloadditions with electron-deficient and electron-rich dipolarophiles. Taken to the extreme, we might even expect to observe a change in the regiochemical preference of a dipole in its reaction with these two classes of dipolarophile. This theoretical prediction has been borne out by experimental observation by a number of researchers.²⁶⁻³⁴ Most significantly, Houk *et al.* have shown that for a range of nitrene 1,3-dipoles, the regiochemistry in the cycloadduct depends on the ionisation potential of both the dipole and the dipolarophile.³⁵ The lower the ionisation potential of the nitrene (that is the more electron-rich), the more likely it is to show this reversal of regiochemistry. The same is true as the ionisation potential of the dipolarophile increases (that is the more electron-deficient), and this phenomenon is exaggerated if both effects are combined.

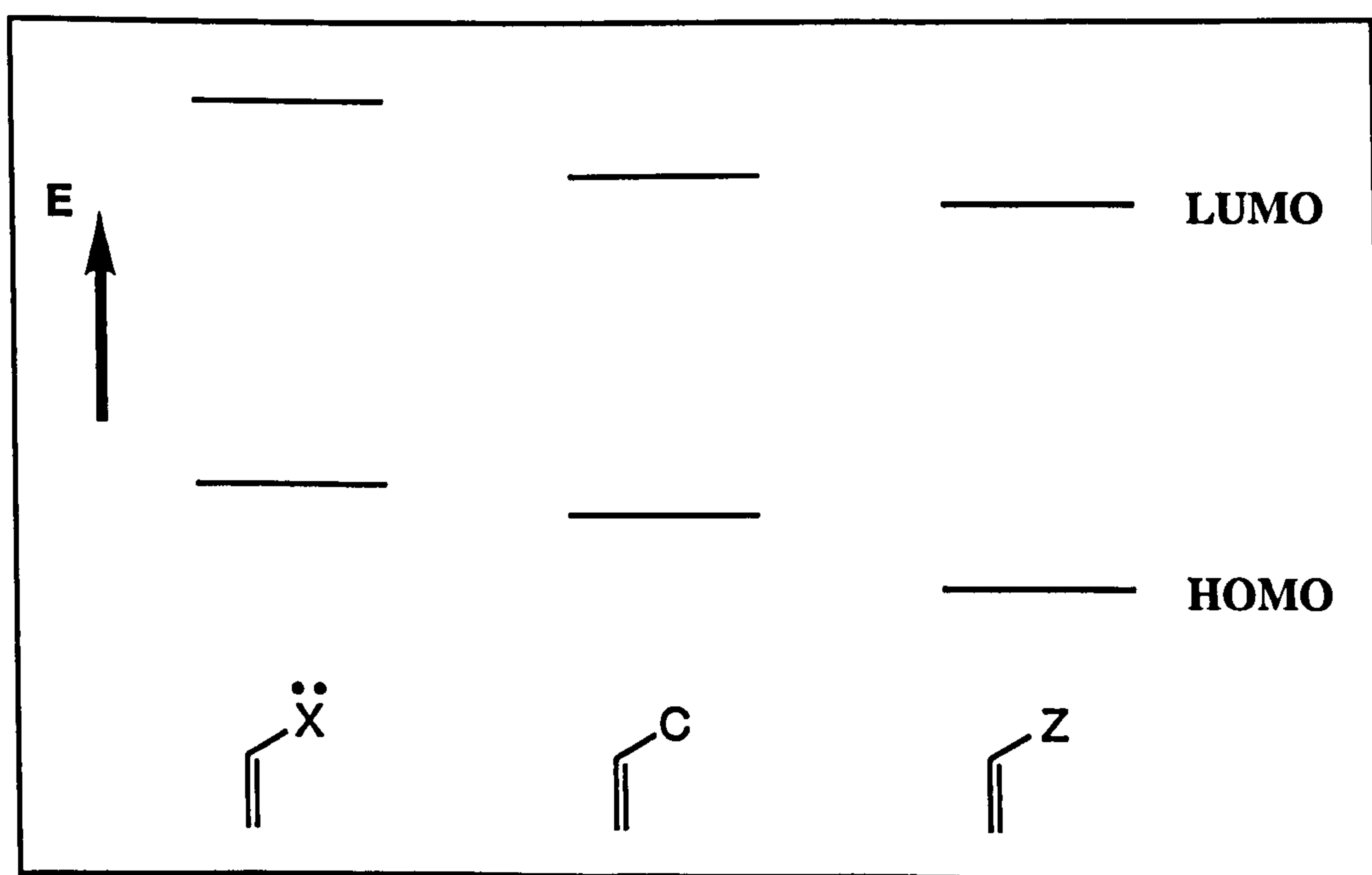


Figure 8 : Relative energies of dipolarophile frontier orbitals.

1.2 Nitroene 1,3-dipoles

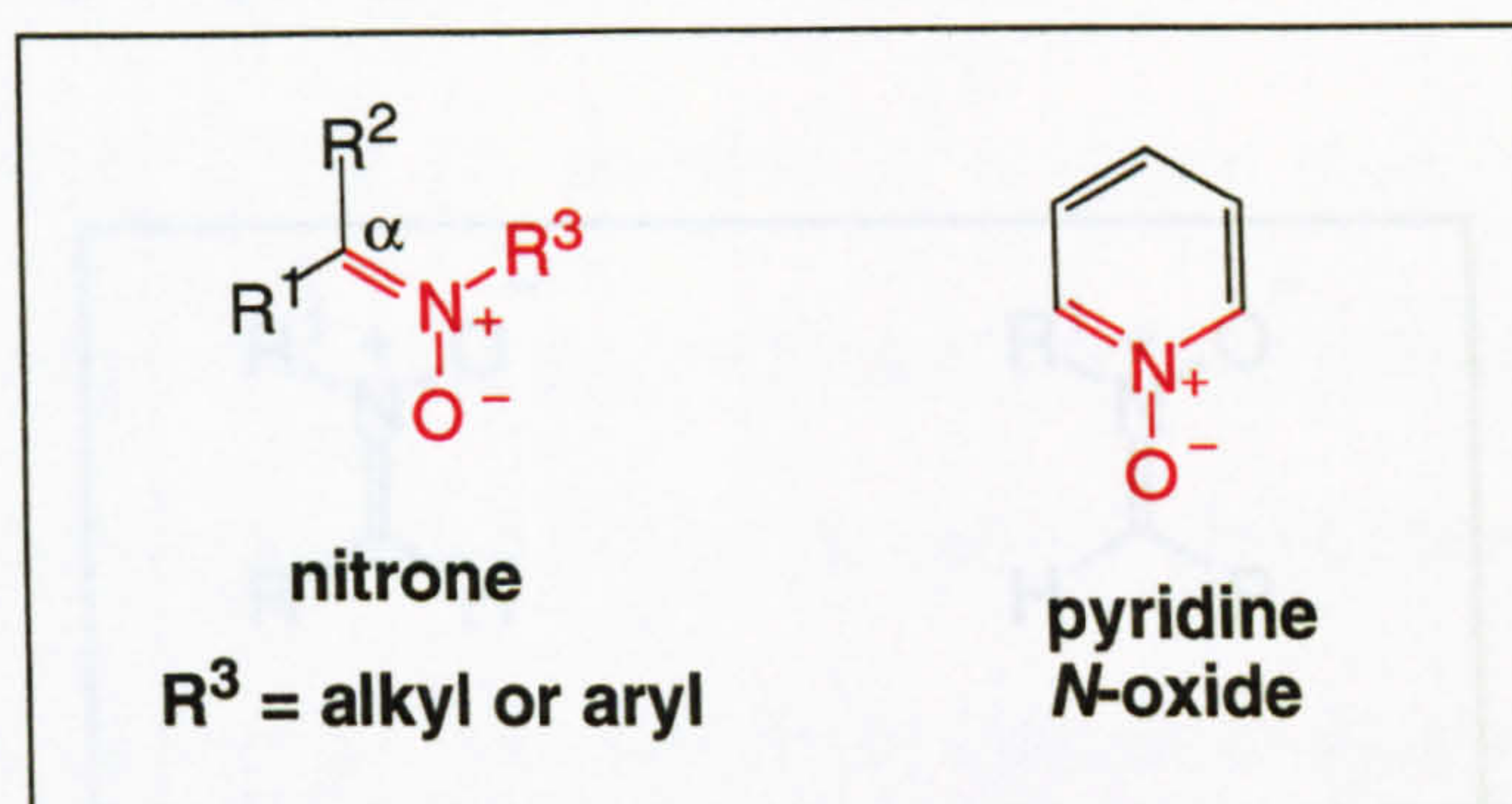


Figure 9 : The nitroene functional group (C=N⁺-O⁻).

Nitrones (or azomethine oxides), Figure 9, were first prepared by Beckmann in 1890^{36,37} and named from a shortening of "nitrogen-ketones" by Pfeiffer in 1916 to emphasise their similarity to ketones.³⁸ Aromatic N-oxides contain the nitroene moiety, but retain the name of the N-oxides whose reactivity they more closely resemble. The general terms aldo- and keto-nitrones are used on occasion, to distinguish between those with and without a proton on the α -carbon respectively. Their chemistry is hugely varied, enough so to be frequently reviewed,³⁹⁻⁴⁸ but as we shall see it is ultimately dominated by their use as 1,3-dipoles for cycloaddition reactions.

1.2.1 Physicochemical properties

Many nitrones are stable at room temperature in air, but rearrangements may occur on prolonged exposure to light. The treatment of nitrones with acid or base leads to cleavage of the double bond to produce a carbonyl compound and an N-substituted hydroxylamine.

Nitrones are slightly basic in character, the pK_a of their conjugate acids most often lying in the range 7-9. N-Methyl-C-phenylnitron, for example, has a pK_a of 8.26.

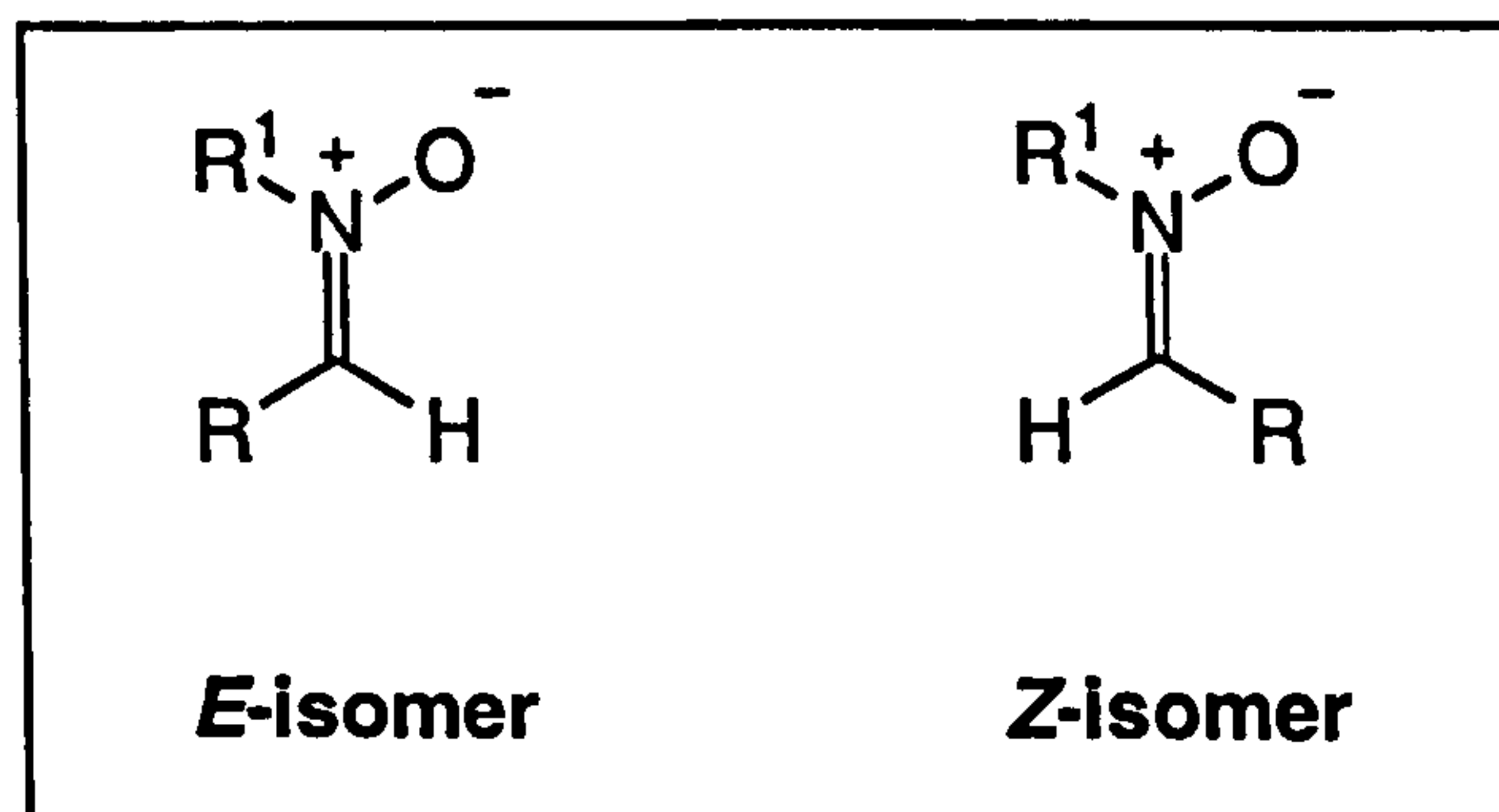
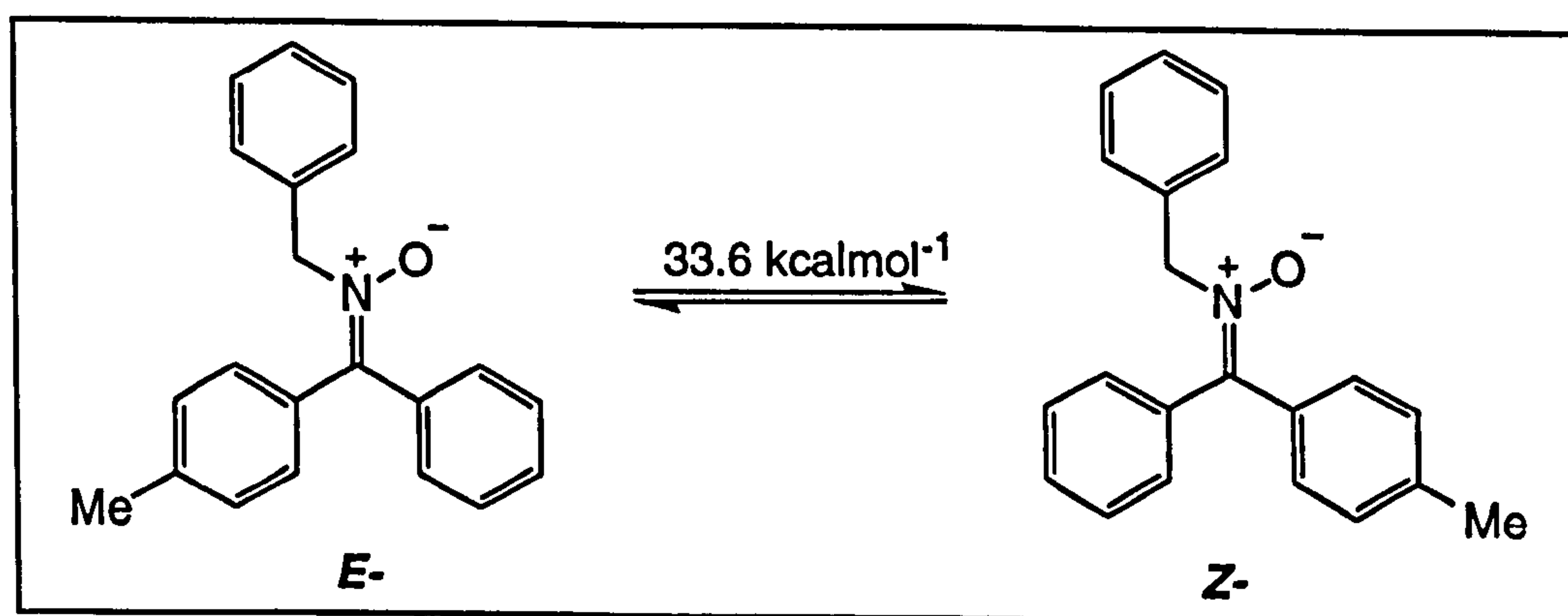


Figure 10 : Geometric isomerism of nitrones.

Because of their double bond, nitrones exhibit geometric isomers, Figure 10, the first example of which was confirmed by dipole moment measurements. The *E*- form is energetically unfavourable, being converted to the *Z*- form by heating. It has been established that aldonitrones exist in the stable *Z*- form; an *E*- aldonitrone, formed from the oxaziridine, was completely isomerised after 24 hours in benzene solution.³⁹ Often this isomerisation can be followed by the change in the NMR spectrum. The activation energy for the isomerisation of *E*- α -phenyl- α -*p*-tolyl-N-benzyl nitrone to the *Z*- form is 33.6 kcal mol⁻¹ (Scheme 1).²⁵



Scheme 1

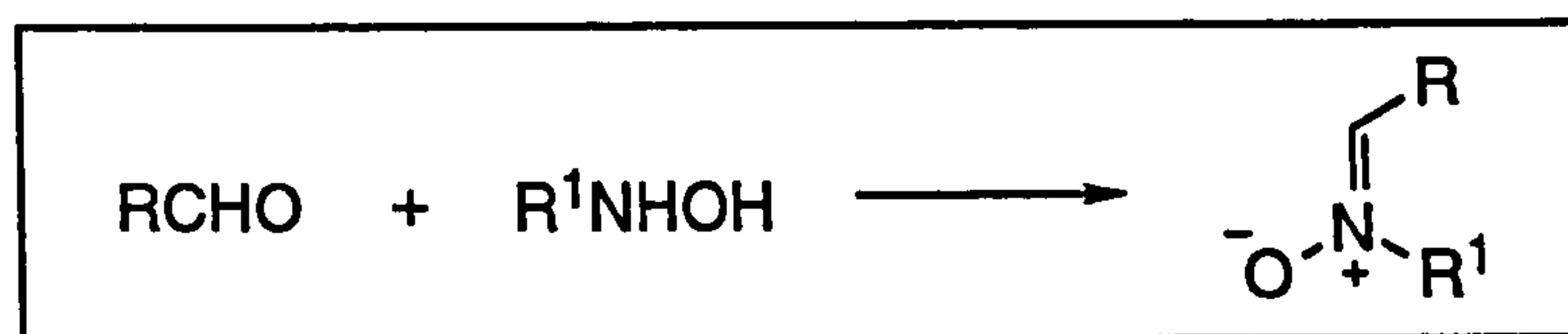
The infrared spectra of aromatic ketonitrones commonly exhibit an N–O stretch between 1200-1280 cm^{-1} (1100 cm^{-1} in aldonitrones), with a C=N stretching frequency in the range 1560-1620 cm^{-1} . The UV spectrum of a nitrone most often shows a strong absorption in the range 230-290 nm, with the intensity increasing with increasing conjugation to the C=N double bond.²⁵ The ^1H and ^{13}C NMR chemical shifts of the two geometric isomers of a nitrone are often sufficiently different to allow discrimination between them, although the assignment of the configuration is most commonly based on dipole-moment measurements. Several groups have studied the mass spectra of variously substituted and deuterated nitrones,⁴⁴ and all exhibit the loss of oxygen (M-16) which is characteristic of N-oxides. The fragmentation patterns are, on the whole, much simpler for negative rather than positive ionisation.

1.2.2 Preparation of nitrones

There are a number of synthetic methods by which nitrones can be prepared. This topic has been reviewed thoroughly,^{25,39-41} so we shall merely consider a few important examples in each of the following groups :

- a. from hydroxylamines and carbonyl compounds
- b. from N,N-disubstituted hydroxylamines
- c. from oximes
- d. from imines
- e. from nitroso compounds

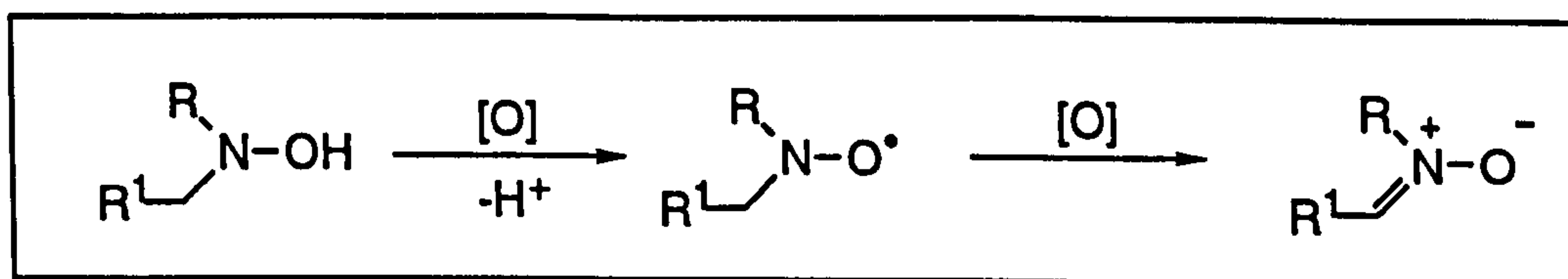
a. from hydroxylamines and carbonyl compounds



Scheme 2

The most common method of preparing nitrones is the condensation of a carbonyl compound and an N-monosubstituted hydroxylamine (Scheme 2). This reaction proceeds in high yield when the N-substituent is alkyl or aryl, and when the carbonyl compound carries non-bulky groups. The nature of the single substituent (R^1) on the hydroxylamine nitrogen has a limited effect on the condensation, but it can affect the isomer ratio of a subsequent 1,3-dipolar cycloaddition reaction. The substituent on the carbonyl carbon (R) will be placed α - to the nitron nitrogen, adding greatly to the range of products available by cycloaddition reactions of these compounds. The carbonyl compounds may also be masked, for example, the synthesis of oxazoline nitrones from orthoesters or amide acetals.

b. from N,N-disubstituted hydroxylamines



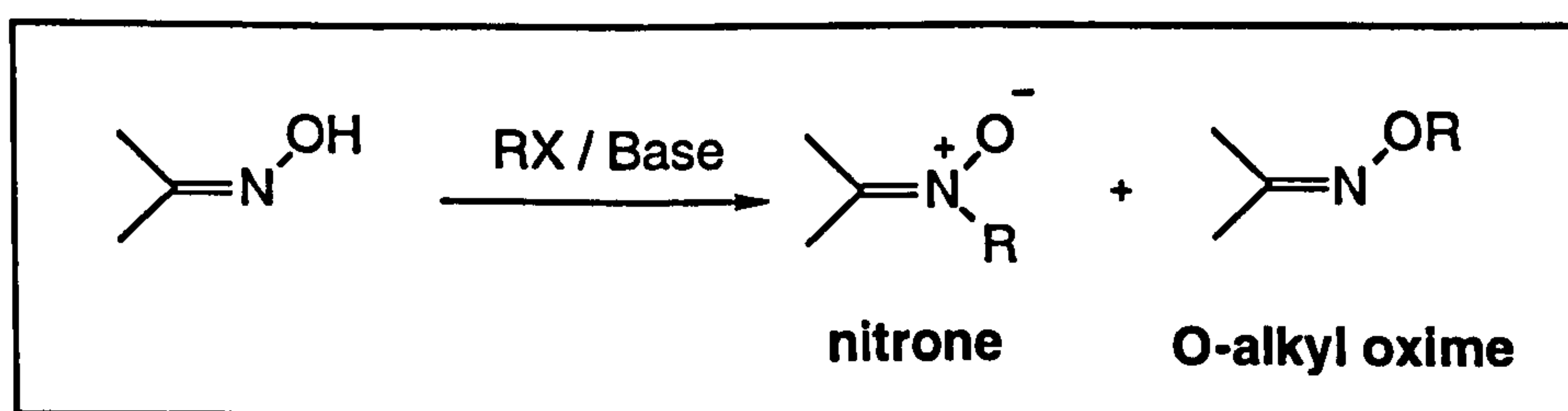
Scheme 3

The preparation of cyclic and acyclic nitrones by dehydrogenation of N,N-disubstituted hydroxylamines has been achieved with any of a number of common oxidants,

including yellow mercuric oxide, lead oxide, potassium ferricyanide, potassium permanganate, potassium dichromate, palladium, peroxides, sodium periodate and salts of copper (II), iron (III) and silver. Oxidation of the hydroxylamine anion to the radical is the first step in the reaction, followed by abstraction of hydrogen (Scheme 3).

c. from oximes

The ambident nucleophilicity of oximes means that the alkylation of oximes can lead to a mixture of the nitron and O-alkyl oxime, the products of N- and O-alkylation respectively (Scheme 4). The alkylating agent (for example, alkyl halides or dialkyl sulphates) and counter ion (for example, Li^+ , Na^+ , Me_4N^+) have a relatively small effect on the product ratio. This problem has been overcome in certain cases by initial conversion to the O-silylated oximes and subsequent reaction with trialkyloxonium tetrafluoroborate.

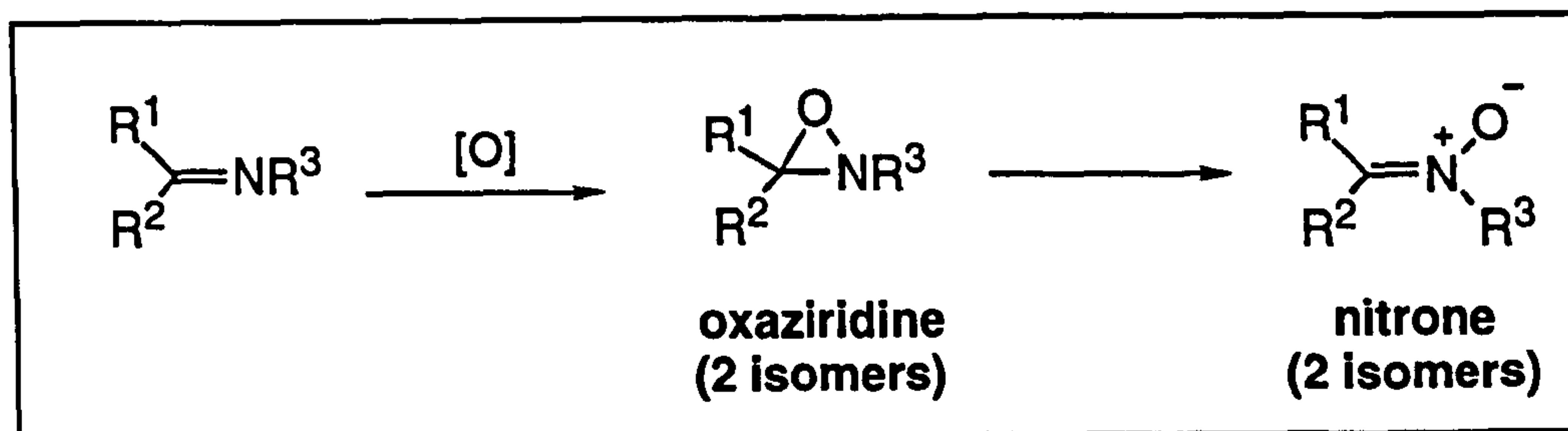


Scheme 4

d. from imines

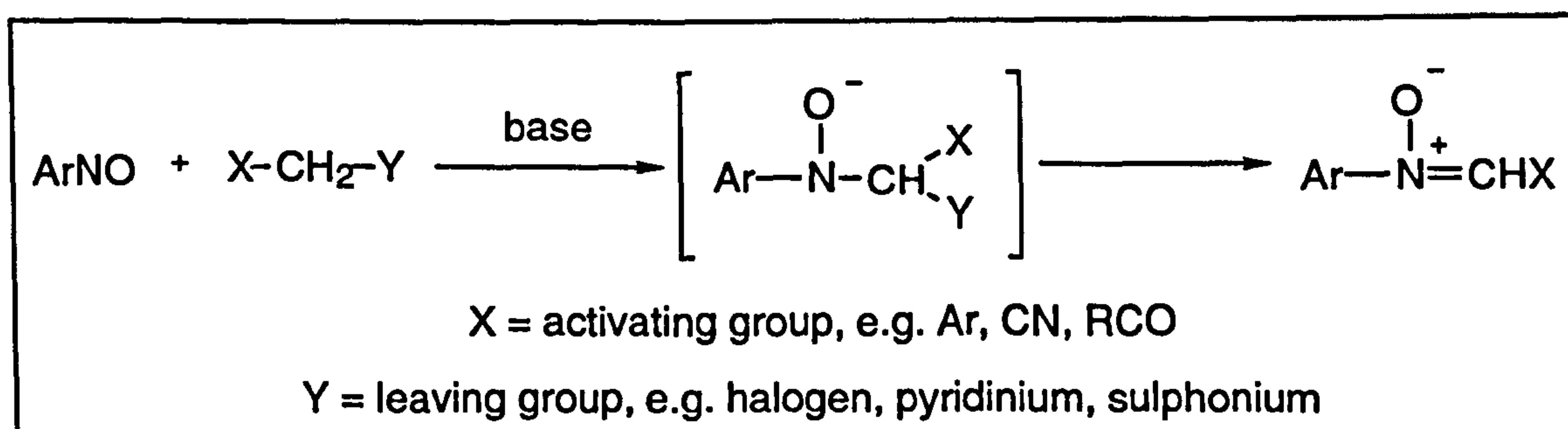
The imine function can be oxidised to a nitron, even when the imine is part of a heteroaromatic system. The most common reagents for this oxidation are peroxycarboxylic acids (for example, peracetic acid, *m*-chloroperbenzoic acid), although other reagents, most notably hydrogen peroxide, are known in the literature. Imines generally give the oxaziridine on oxidation, which is then isomerised to the nitron (Scheme 5), but the conversion may be

direct in some instances. Attempts to thermally isomerise some oxaziridines has led not to the desired nitrones, but to a variety of rearrangement products, predominantly amides.³⁹



Scheme 5

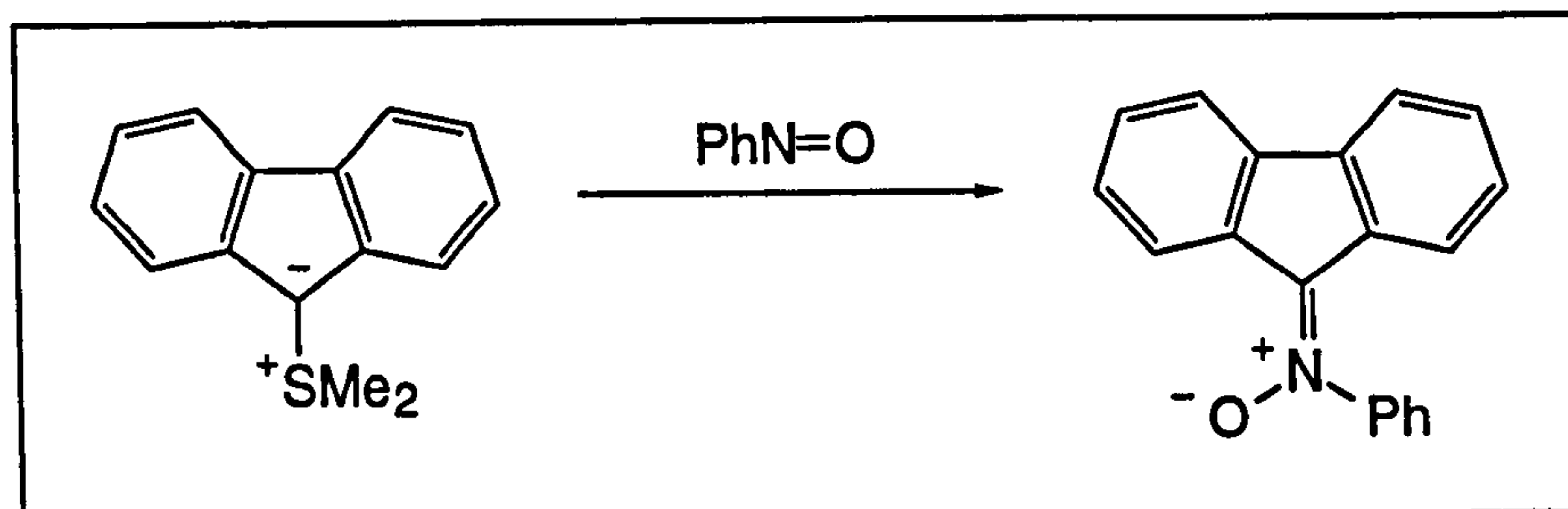
e. from nitroso compounds



Scheme 6

The reaction of an aromatic nitroso compound with a compound containing an activated methylene group, in the presence of catalytic base, leads to a mixture of nitrones and imines. Yields can be high without contamination using the Kröncke reaction (Scheme 6), in which the methylene group is attached to the nitrogen of a pyridinium salt. In principle, the methylene requires an activating group (for example, aryl, cyanide or isocyanate) and a good leaving group (for example, pyridinium, sulphonium or halogen).^{25,39}

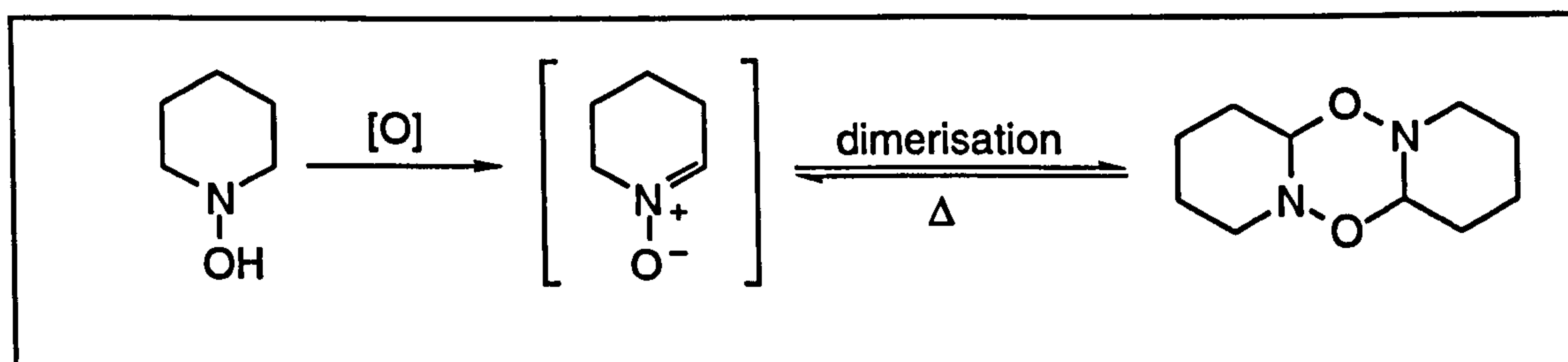
An example is the reaction of 9-dimethylsulfoniumfluorenylide with nitroso benzene to afford the corresponding N-phenyl nitrone in quantitative yield (Scheme 7).



Scheme 7

1.2.3 Reactions of nitrones

a. Dimerisation



Scheme 8

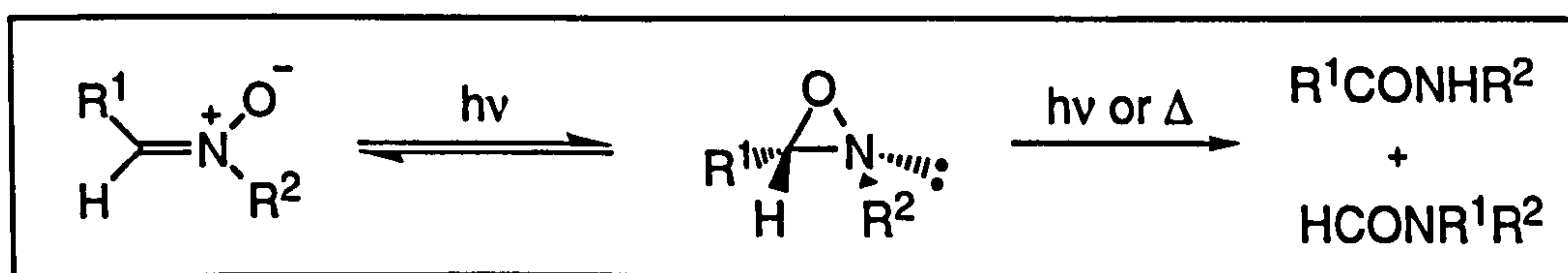
It has been observed that oxidative routes to certain nitrones lead to the isolation of the nitronium dimer or trimer. For example, the mercuric oxide oxidation of N-hydroxypiperidine gives the dimer (Scheme 8) or even the trimer, whereas the oxidation of N-hydroxypyrrolidine affords the monomeric nitronium only. It seems that certain of the more reactive nitrones are susceptible to these association reactions, although this can be controlled

by preparing the nitron in solution. Alternatively, the dimer or trimer may be thermally cracked, to give the desired monomeric nitron.

b. Rearrangements

i) Photolysis

Nitrones undergo photochemical isomerisation into oxaziridines *via* a disrotatory cyclisation (Scheme 9). The oxaziridines may undergo further photochemical or thermal reaction to produce the amide by migration of one substituent from the “nitron” carbon atom to the nitrogen atom. The reverse reaction - isomerisation of oxaziridines to the nitron with, for example, silica gel or heating, is a popular nitron synthetic route. The presence of substituents on the nitron will affect the feasibility of these reactions. It has been shown that 2-unsubstituted pyrroline-N-oxides and the 2,5,5-trimethyl analogue formed the oxaziridine, whereas the 2-substituted isomers did not.^{39,40} A radical mechanism has been postulated as being the most likely for oxaziridine formation.

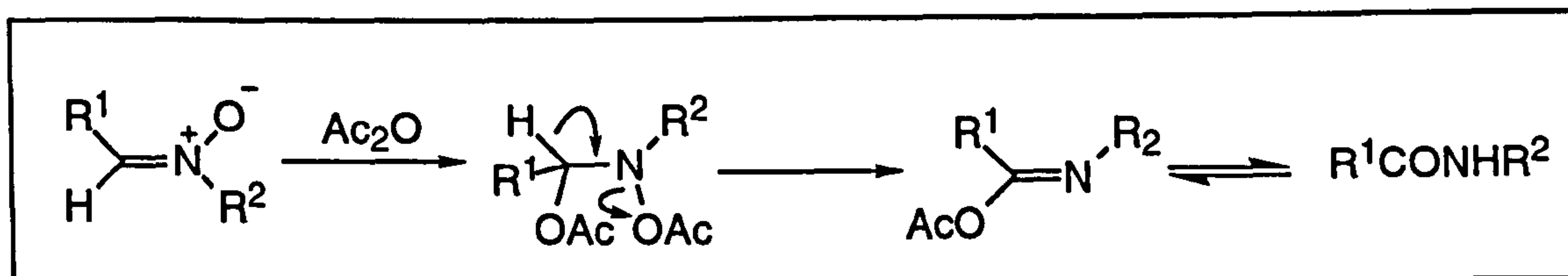


Scheme 9

ii) Amide formation

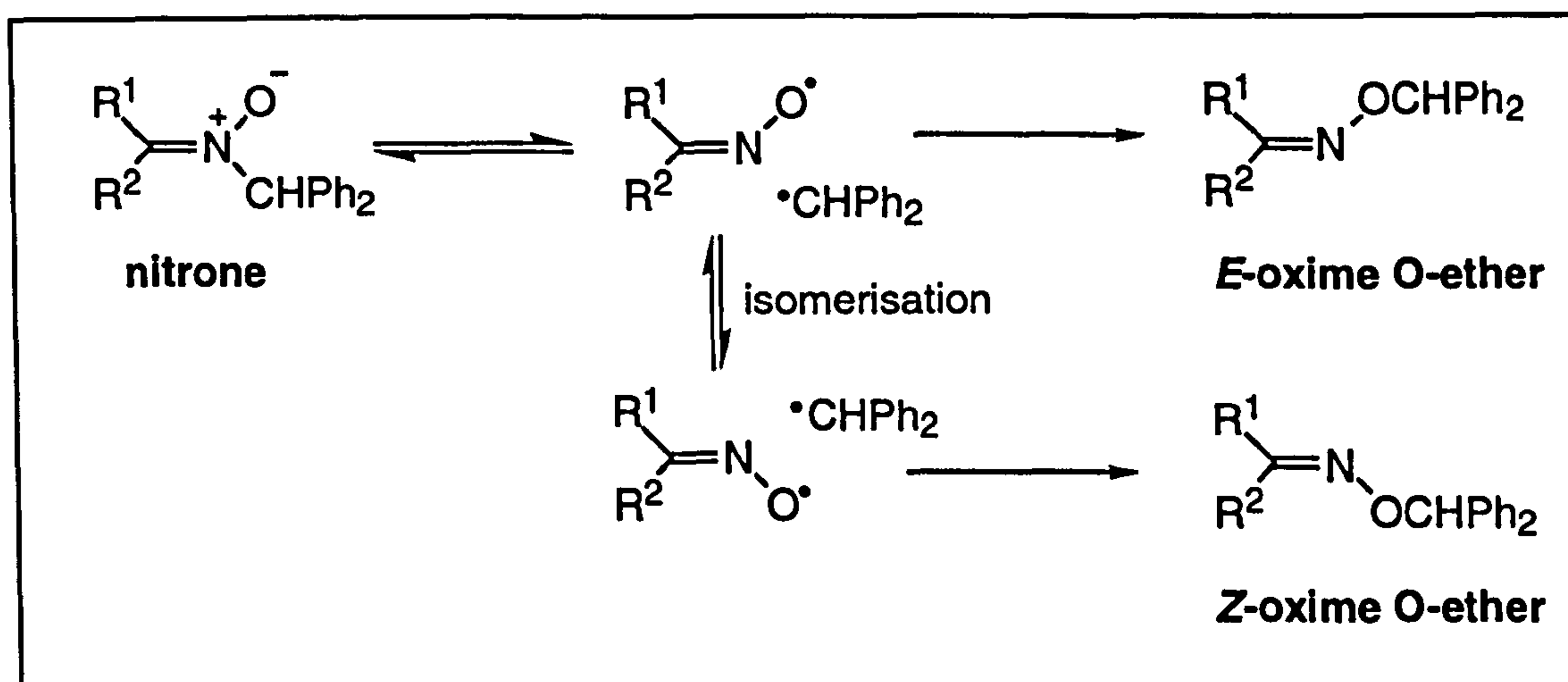
As well as photolytic rearrangements, nitrones may also be rearranged to amides by a number of chemical means. The list of reagents includes phosphorus pentachloride, acetyl chloride, sulphur dioxide and bases in ethanolic solution; yields are often high. However, the most effective reagents are phosphorus trichloride (though this may deoxygenate the

nitron), phosphorus oxychloride and acetic anhydride. Kröhnke has put forward two mechanisms to explain those reactions in which rearrangement occurs with and without migration of substituents. The proposed migration-free mechanism of amide formation with acetic anhydride is shown in Scheme 10.



Scheme 10

iii) Isomerisation to oxime O-ethers.

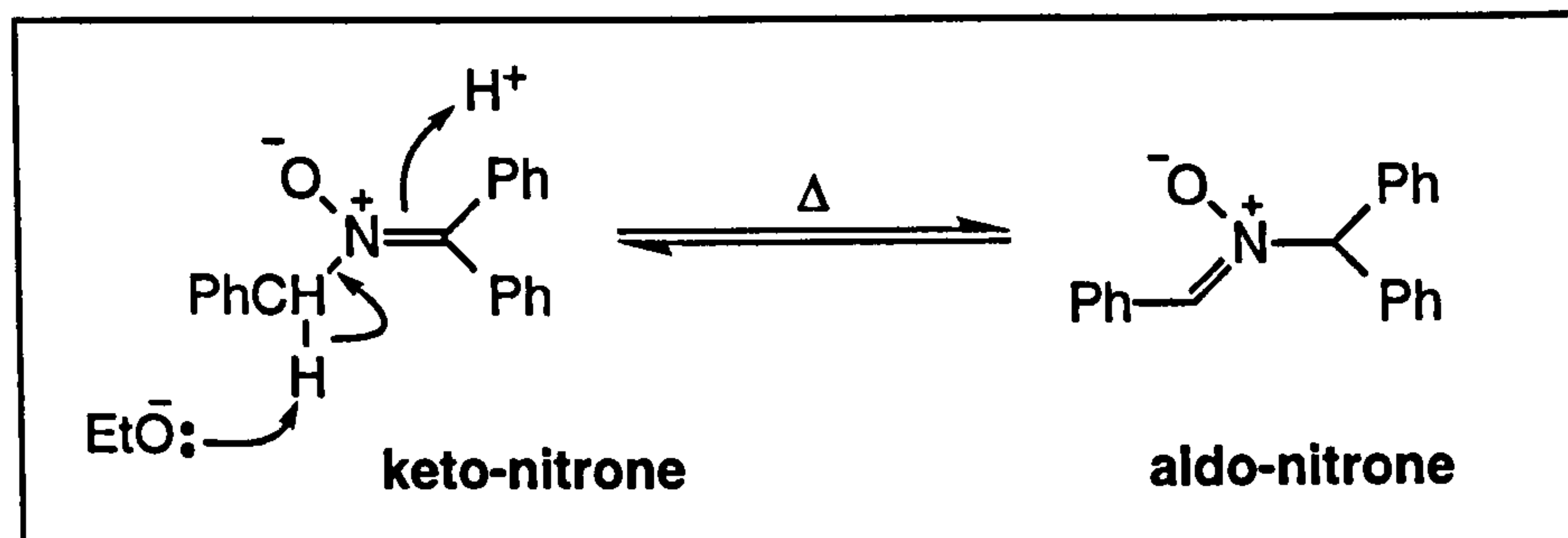


Scheme 11

Certain nitrones are converted into oxime O-ethers by heating, but the reaction is not general. Thermolysis of N-(diphenyl)methyl nitrones proceeds *via* isomerisation of the iminoxy radicals (Scheme 11). The radical intermediacy has been proven by *chemically induced dynamic nuclear polarisation* (CIDNP),⁴⁹ as well as the generation of crossover

products.²⁵ Geometric isomerisation of the iminoxy radicals leads to formation of the *E*- and *Z*- isomers of the oxime ether.

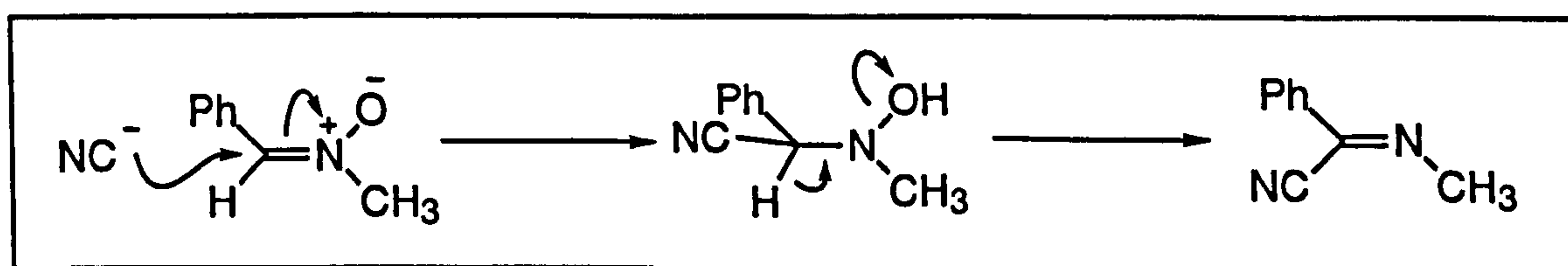
iv) **Behrends rearrangement**



Scheme 12

The rearrangement of nitrones may be effected by catalytic base, in which the double bond is moved to favour the isomer with the lowest energy. Thus, it has been shown that many ketonitrones rearrange into the more stable corresponding aldonitrone isomer (Scheme 12).

c. **Addition of Nucleophiles.**

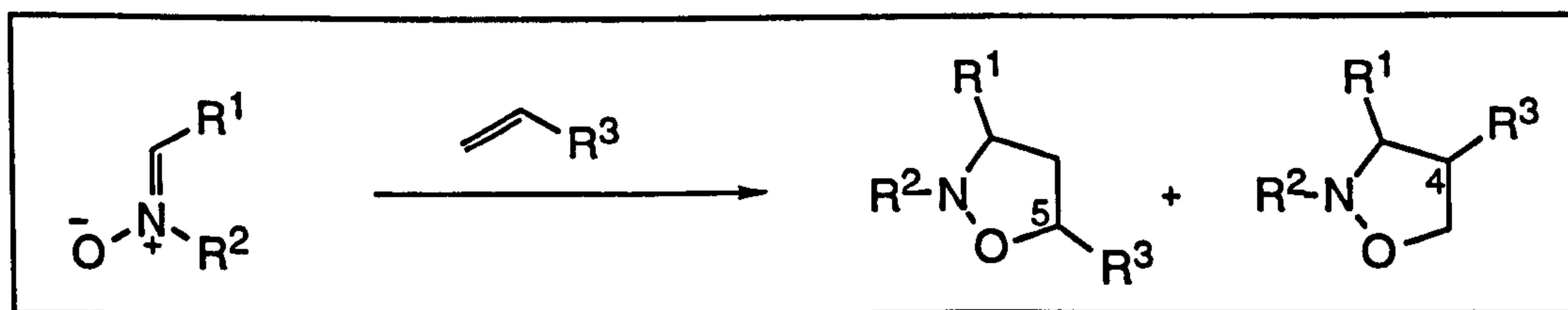


Scheme 13

A number of nucleophiles add to the carbon terminus of nitrones to form α -substituted hydroxylamines, as for example, in acid or base-catalysed hydrolysis. The

isolated products depend on the nucleophile in question, as many adducts undergo secondary reactions. Hydrogen cyanide adds to aldonitrones to yield α -cyano-hydroxylamines, which can then eliminate water, producing α -cyanoimines (Scheme 13). These imines may react with a second molecule and cyclise to the imidazoles, a process promoted by the addition of a thiol. Carbanions, active methylene compounds, ylides and organometallic compounds have been added to nitrones. Ketonitrones may be less reactive to nucleophilic addition than aldonitrones, for example, they often resist the addition of Grignard reagents, being reduced to imines, but most addition reactions are general.

d. 1,3-Dipolar cycloadditions.



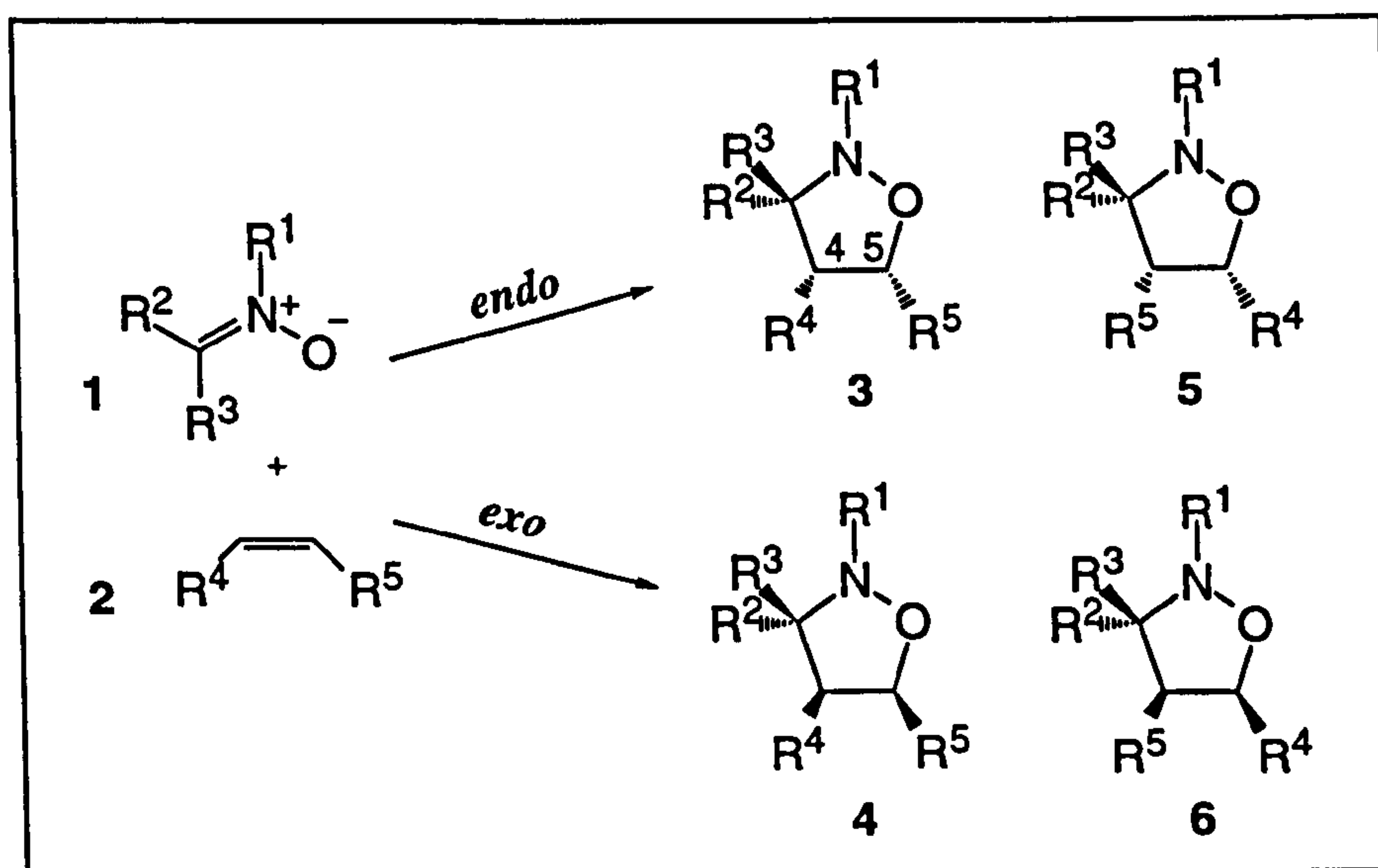
Scheme 14

The chemistry of nitrones is dominated by their use as 1,3-dipoles in cycloaddition reactions. Cyclic and acyclic nitrones have been reacted with a range of dipolarophiles including alkenes to afford the isoxazolidine cycloadducts (Scheme 14) as well as alkynes and isocyanates (Section 1.1.2). It has been demonstrated that the cycloaddition reaction can exhibit high stereo- and regioselectivity (Section 1.1.3). In the cycloaddition reactions of simple alkyl and aryl nitrones the 5-substituted isoxazolidine cycloadducts are commonly the predominant regioisomers. However, as we shall see in the following section, there is much potential for predicting and controlling the stereochemical outcome of these reactions and this

has led to the widespread use of nitrene cycloadditions in the synthesis of a number of biologically important molecules.

1.3 Asymmetric 1,3-dipolar cycloaddition reactions of nitrones

1,3-Dipolar cycloaddition reactions have long been recognised as possessing the potential for high stereo- and regio-control, and the number of natural product total syntheses utilising the 1,3-dipolar cycloaddition reactions of nitrones as a key step testifies to their usefulness. In the reaction of a nitrone **1** with a disubstituted alkene **2**, three new contiguous chiral centres are generated in the isoxazolidine cycloadducts (Scheme 15).



Scheme 15

It is clear from Scheme 15 that there are two regiochemical senses of addition as well as either *exo* or *endo* approach of the two components, leading to two pairs of regioisomeric and diastereomeric products. Thus, whilst **3** and **4** have the same regiochemistry, they are formed *via* the *endo* and *exo* transition states, respectively, and this is reflected in the differing stereochemistry at C-4 and C-5. Similarly, whilst **5** and **6** arise from cycloaddition in the same regiochemical sense, they, too, are formed from the *endo* and *exo* transition states, respectively. However, the nitrone **1** also has two faces, each of which may be

involved in the cycloaddition and so we must also consider the formation of the enantiomers of all four products. These structures can be realised by inversion of the stereochemistry at C-3 in each of the cycloadducts 3-6. The likelihood of obtaining a single product from so many possibilities may seem remote, but a wealth of experimental evidence has allowed certain rules-of-thumb to be drawn up. For example, the relative stereochemistry at C-4 and C-5 in the isoxazolidine is controlled by the choice of the alkene dipolarophile. The geometry of the alkene substituents determines, without exception, the relative stereochemistry at the corresponding positions in the isoxazolidine. For example, we can predict that, as R⁴ and R⁵ are *cis*- in the alkene, they will be *cis*- in the products.

In the absence of over-riding steric factors, the Frontier Molecular Orbital theory provides a reliable guide to the regiochemical outcome of the reaction of an alkene with a nitron (Section 1.1.4). The *endo* or *exo* preference is harder to predict, as it depends on the steric bulk of the nitron and alkene, as well as on any secondary orbital interactions that may be present in the transition state. The facial nature of the nitron, as with other 1,3-dipoles, provides the potential to restrict reactivity to just one of the two possible faces. Thus, a chiral substituent on the nitron may sterically hinder the approach of the alkene to one face, favouring the formation of one particular enantiomer of the product.

As we shall see, asymmetric induction in 1,3-dipolar cycloaddition reactions with chiral nitrones can be an effective strategy (Section 1.3.1) and many experimenters have also found success using alkenes that carry the chiral information (Section 1.3.2).⁵⁰ It is clear from the recent literature that interest in the application of chiral catalysis to cycloaddition reactions has blossomed in the past few years (Section 1.3.3). We shall examine a selection of examples in each case, as all three of these induction strategies have been recently thoroughly reviewed.^{51,52} Firstly, we shall examine the literature on 1,3-dipolar

cycloadditions of chiral nitrones - an area that we shall consider in three parts: the reactions of nitrones with the chiral group (*R) attached to the carbon atom (7), to the nitrogen atom (8), and chiral cyclic nitrones (9) (Figure 11).

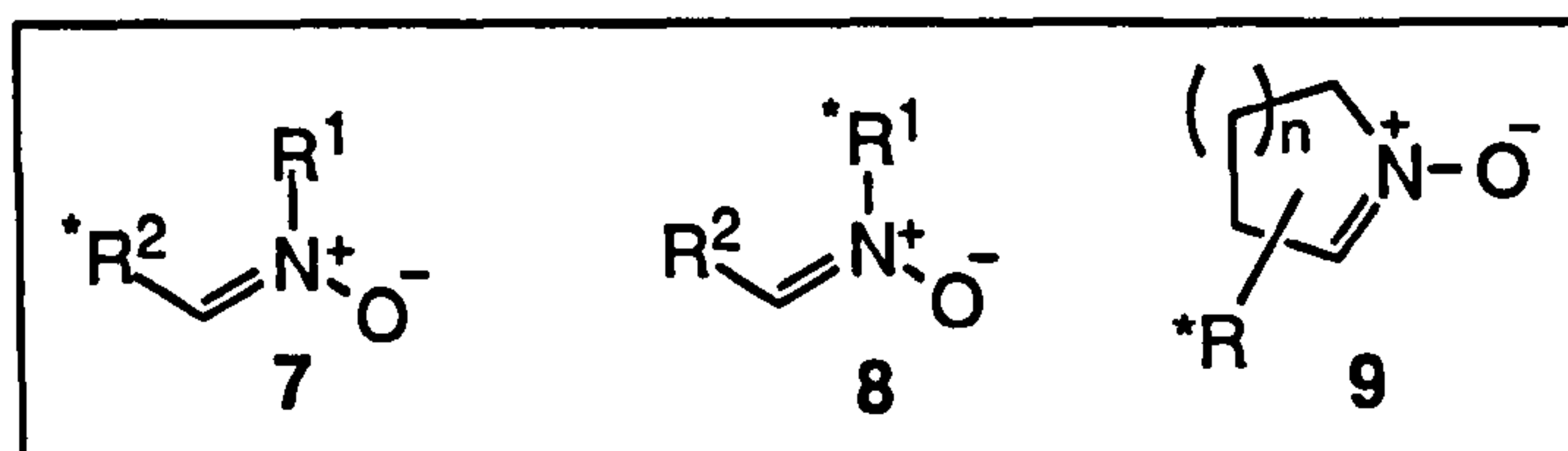
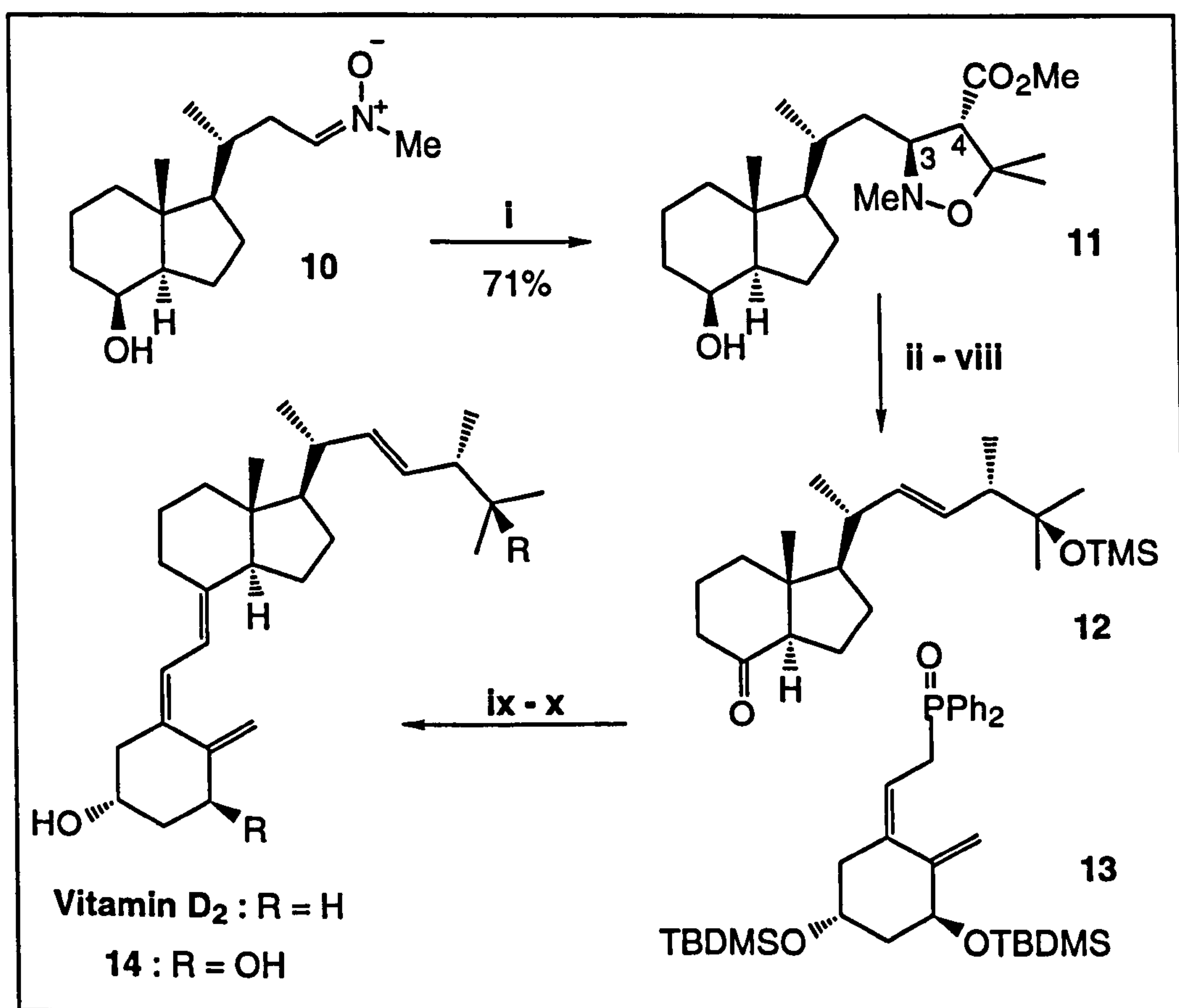


Figure 11

1.3.1 Chiral nitrones in 1,3-dipolar cycloaddition reactions

The availability of chiral nitrones by various short synthetic routes, often from abundant enantiopure natural materials, has allowed their application to the total synthesis of diverse chemical targets. One of the most impressive syntheses utilising nitrones bearing the chirality on the carbon atom is the preparation of analogues of cholecalciferol (Vitamin D₃) and ergocalciferol (Vitamin D₂) by Baggiolini *et al.* (Scheme 16).^{53,54} The chiral nitrone **10** was prepared from the corresponding aldehyde, which ultimately derived from a known chiral keto-acid intermediate. The 1,3-dipolar cycloaddition reaction of **10** with methyl 3,3-dimethylacrylate afforded the desired (3*S*, 4*S*)-isoxazolidine product **11**, which was separated from a 1:1 mixture with the (3*R*, 4*R*)-isomer. The unwanted isomer was thermally isomerised in xylene at 140°C to give the desired cycloadduct **11** in yields of up to 71%. Reduction of the ester and quaternisation of the nitrogen atom of isoxazolidine **11**, cleavage of the N-O bond with Hoffmann elimination and oxidation gave the desired non-nitrogenous

ketone **12**. The phosphine oxide **13** underwent a Wittig-Horner reaction with **12** and, after desilylation with TBAF, the Vitamin D₂ analogue **14** was isolated.⁵⁴

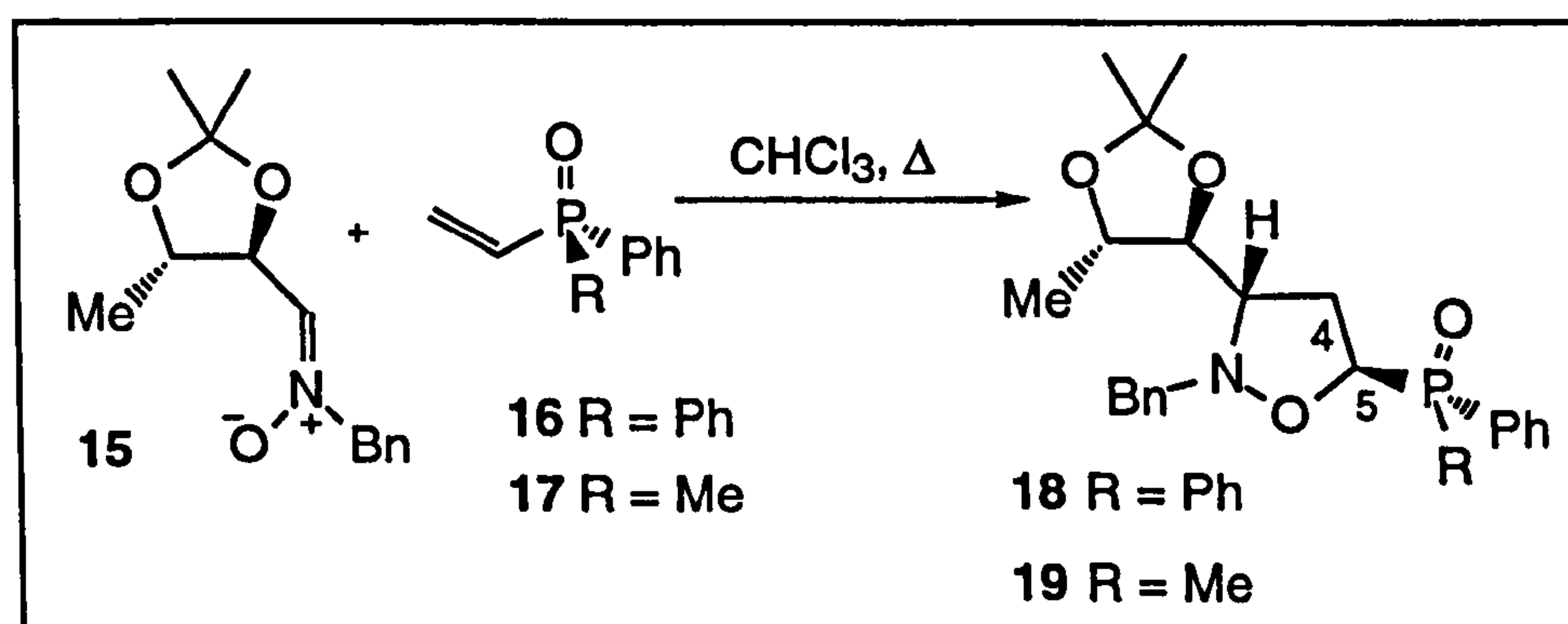


Reagents : i, xylene, Me₂C=CHCO₂Me, 140°C; ii, LiAlH₄, THF; iii, *p*-TsCl, pyridine; iv, LiAlH₄, THF, Δ; v, MeI, toluene, 60°C then Zn, AcOH; vi, MeI, toluene, 70°C then ^tBuOH, ^tBuOK, Δ; vii, PCC, DCM; viii, N-TMS-imidazole, THF; ix, *n*-BuLi, THF, -78°C; x, TBAF, THF.

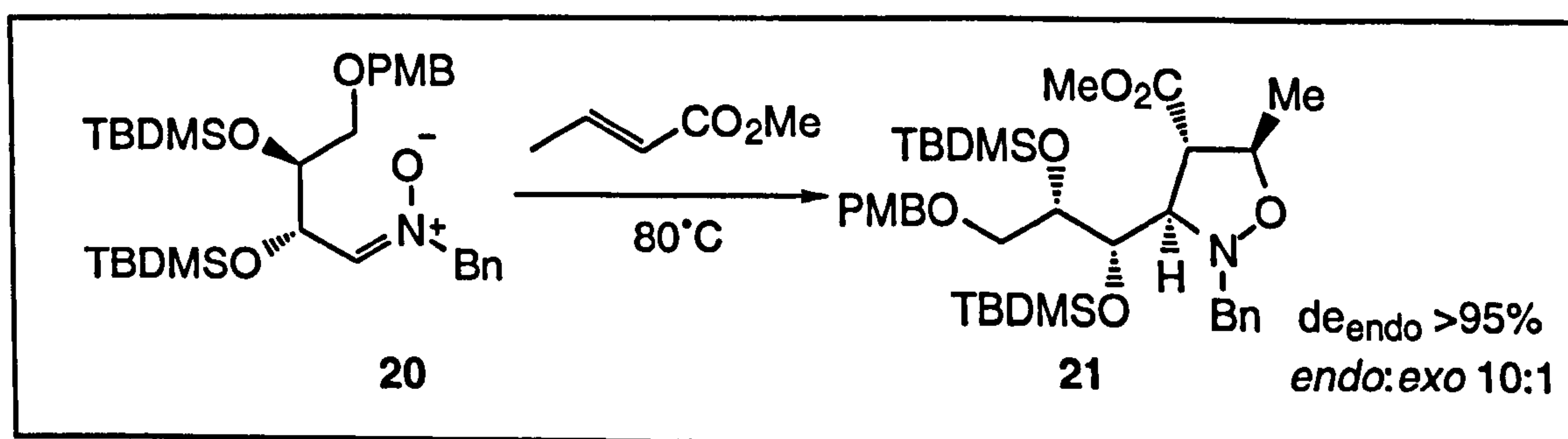
Scheme 16

Brandi has also studied the 1,3-dipolar cycloaddition of facially differentiated α,β-dialkoxynitrones with vinylphosphine oxides (Scheme 17).⁵⁵⁻⁶⁰ The homochiral nitrone **15** shows high diastereofacial selectivity in its cycloaddition with vinylphosphine oxides **16** and **17**. In the reaction of **16** with **15**, the *endo* diphenylphosphinyl isoxazolidine isomer **18** is the major product, but it is formed along with the *exo* isomer and the 4-regioisomer in a ratio

of 63:12:21 after 10 hours reflux in chloroform. Exchange of one of the phenyl groups on phosphorus in **16** for methyl enforces a double asymmetric induction strategy, and leads to the isolation of the isoxazolidine **19** (75%) after 7 days at room temperature. The *endo:exo* ratio is now 95:5, with no observed formation of the 4-regioisomer and a small increase in the diastereomeric excess of the *endo* product to an impressive 96%.⁵⁵ A racemate of nitron **15** has been reacted with vinyl ester and ether dipolarophiles by De Shong.^{61,62} Reaction proceeds with high *endo*-selectivity, as well as high diastereofacial selectivity, to generate an intermediate in the synthesis of the amino-sugar daunosamine. Similar nitrones have been used by Thomas to give essentially one isoxazolidine isomer in a 1,3-dipolar cycloaddition with methyl crotonate.⁶³



Scheme 17



Scheme 18

Saito *et al.* have developed homochiral nitrones, such as **20**, derived from threitol (Scheme 18).^{64,65} Nitron **20** was found to give predominantly the *endo* isoxazolidine **21** (*endo:exo* 10:1) in a 1,3-dipolar cycloaddition reaction with methyl crotonate, with high diastereofacial selectivity.

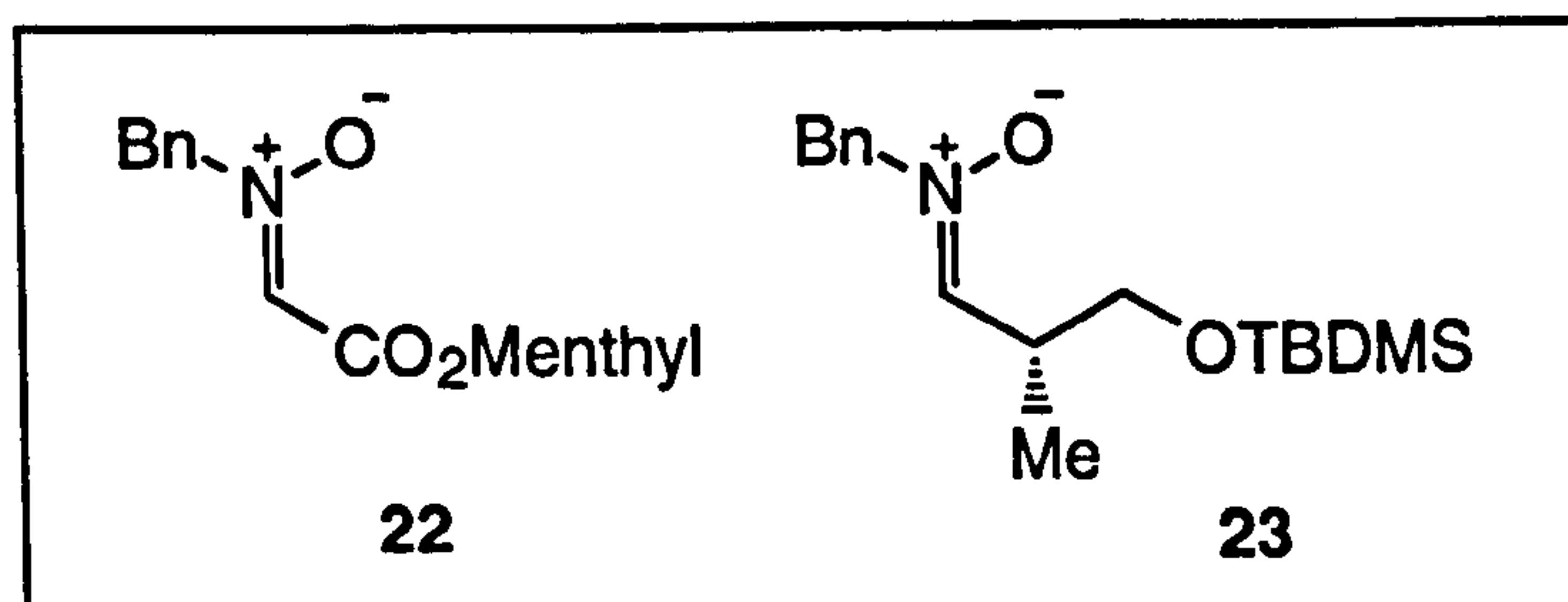
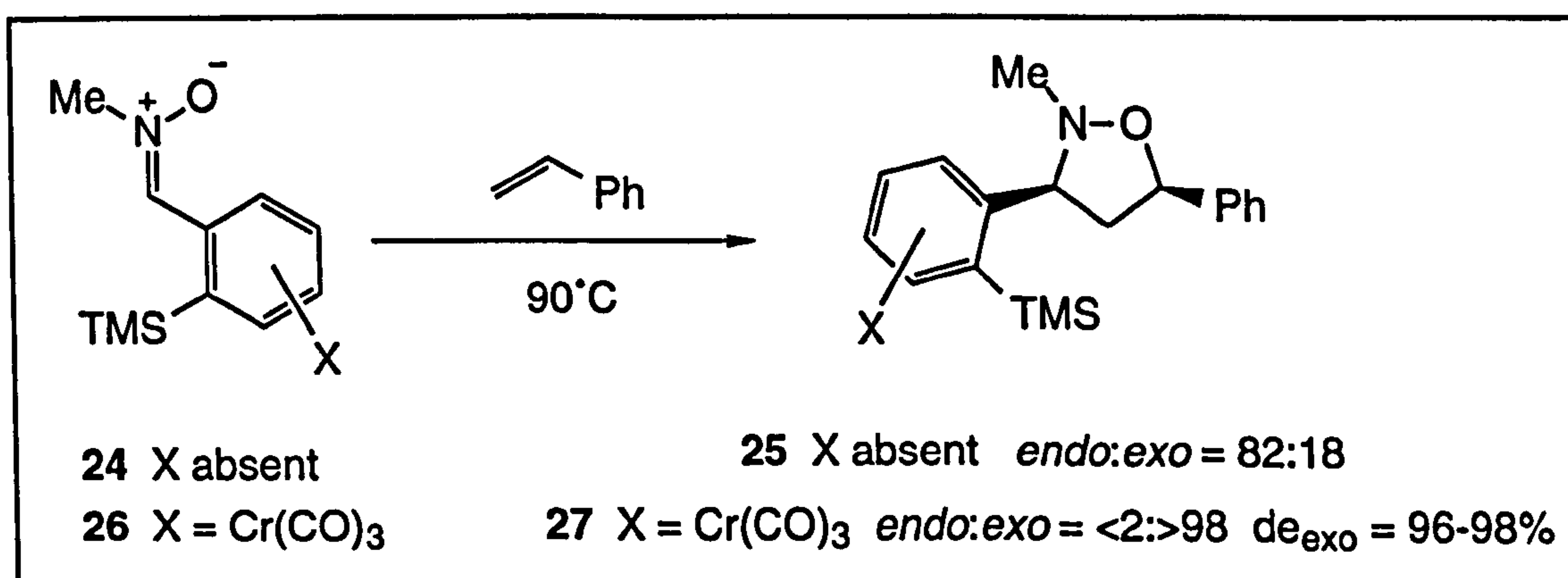


Figure 12

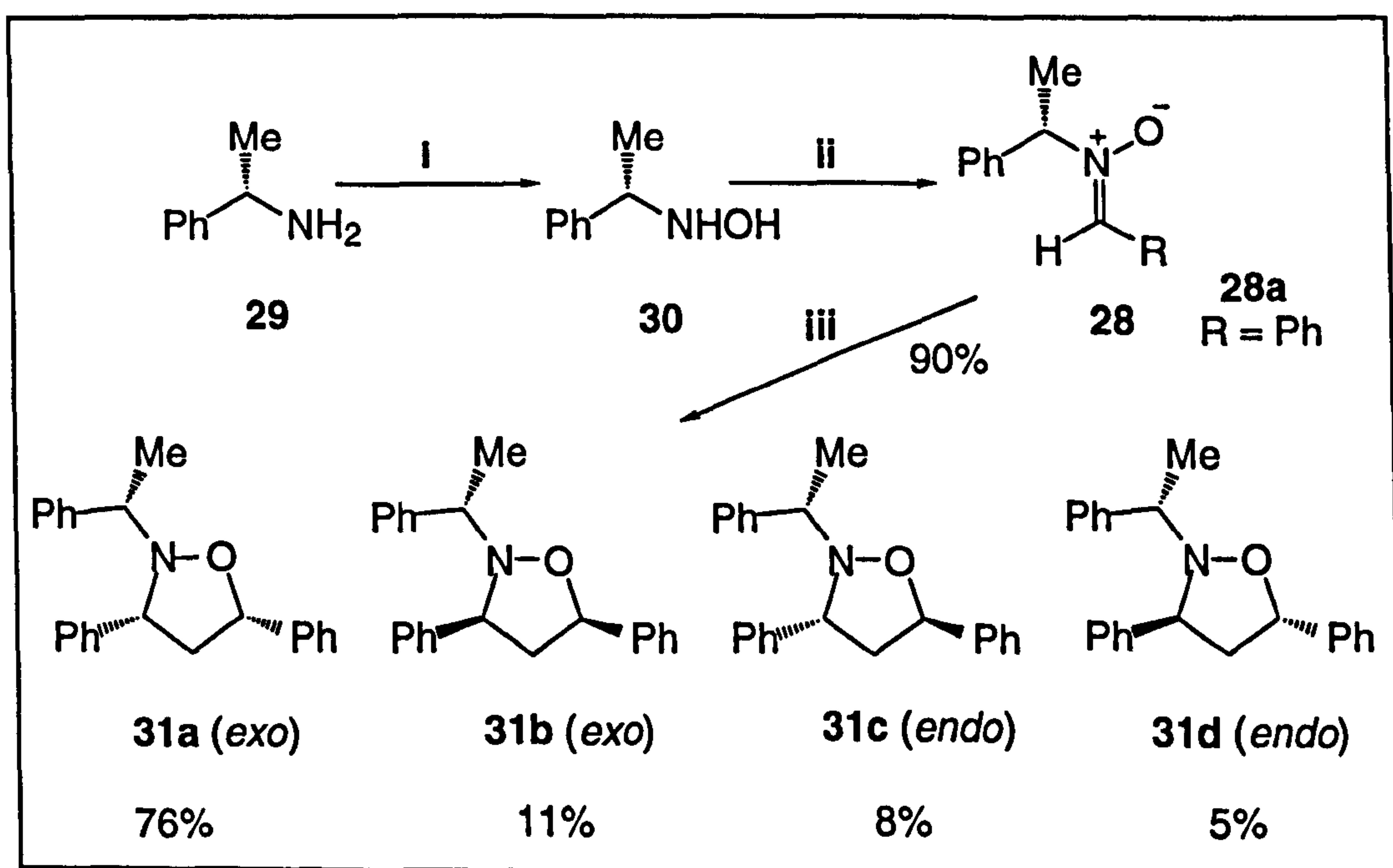
Amongst other nitrones with the chiral centre attached to the nitron carbon atom are the N-benzyl nitrones developed by Kametani **22**⁶⁶ and Ito *et al.* **23** (Figure 12).⁶⁷ However, these two nitrones both give rise to a mixture of diastereoisomers in their 1,3-dipolar cycloaddition reactions with benzyl crotonate.



Scheme 19

Mukai *et al.* have investigated the use of chromium tricarbonyl-derived nitrones with a number of alkene dipolarophiles (Scheme 19).^{68,69} The nitron 24 reacts with styrene at 90°C to give the isoxazolidine 25 as a mixture of *endo* and *exo* diastereoisomers in the ratio 82:18 respectively. The related chromium tricarbonyl-substituted nitron 26 by contrast, gives the *exo* isomer of isoxazolidine 27 as the only observed product. The authors explain their observations by the ability of the chromium tricarbonyl moiety to shield one face of the nitron, which then leads to very high diastereofacial induction (de_{exo} of 96-98%).

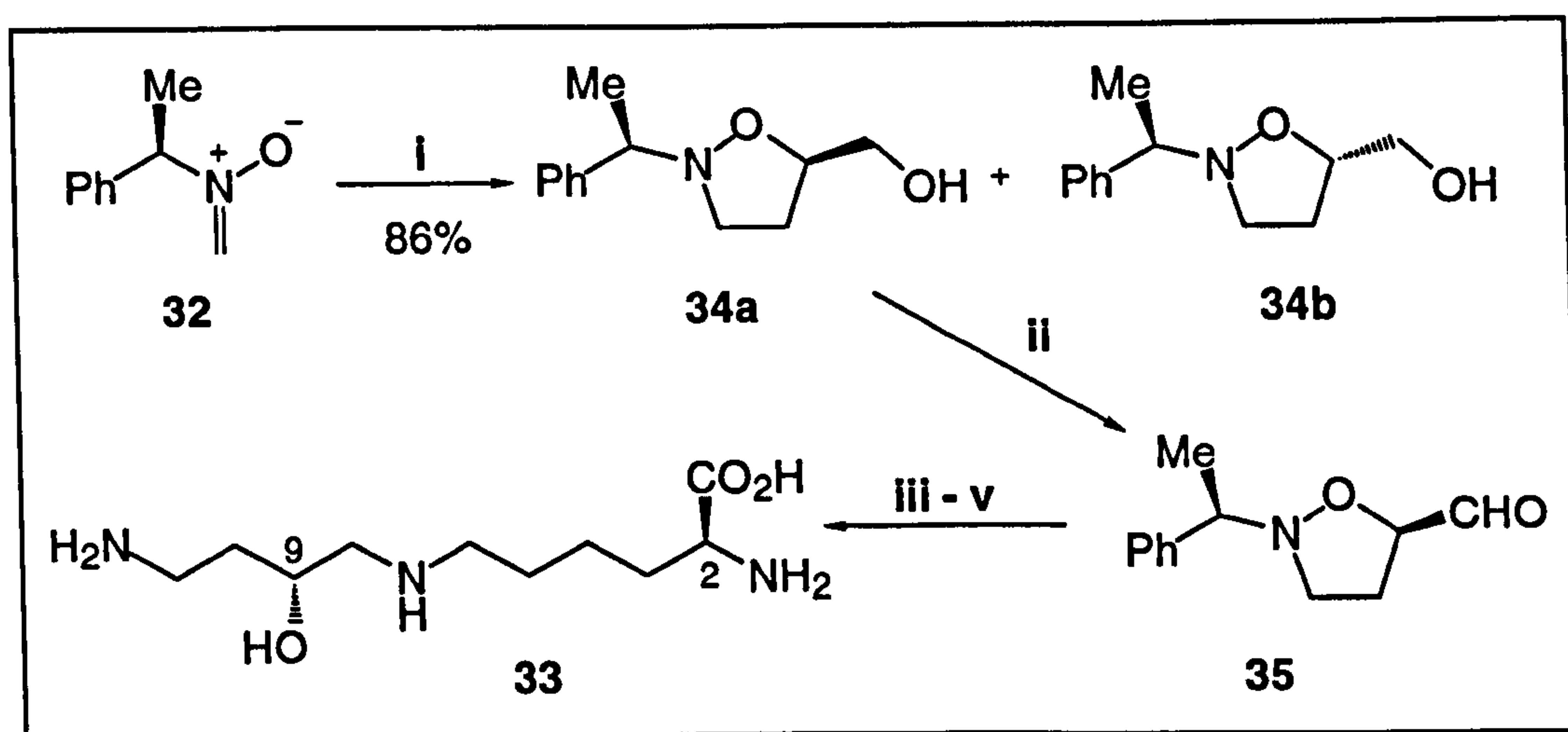
The most common chiral substituent on the nitrogen atom of the nitron is the 1-phenylethyl group, the corresponding nitrons 28 being formed from 1-phenylethylamine 29 (both enantiomers are available optically pure) *via* the hydroxylamine 30. In 1,3-dipolar cycloadditions with styrene, 28a gave predominantly the *exo* isoxazolidine isomers 31a & 31b with fair to excellent diastereofacial selectivity (Scheme 20).^{70,71}



Reagents : i, (PhCO)₂O₂; ii, PhCHO, C₆H₆; Δ iii, CH₂=CHPh, C₆H₆, Δ, 15h.

Scheme 20

Tice and Ganem used a similar nitron **32** in the synthesis of the polyamine bovine brain extract (+)-hypusine **33** by cycloaddition with allyl alcohol, which gave a 1:1 mixture of two diastereomers **34a** and **34b** (Scheme 21).⁷² Swern oxidation of **34a** to afford the aldehyde **35** was followed by reductive amination with a derivative of lysine and exhaustive hydrogenation to yield the natural product **33**. In a similar fashion, the enantiomer of nitron **32** was used to furnish the enantiomer of **35** and so afforded non-natural 9-epihypusine [(9*S*)-**33**].

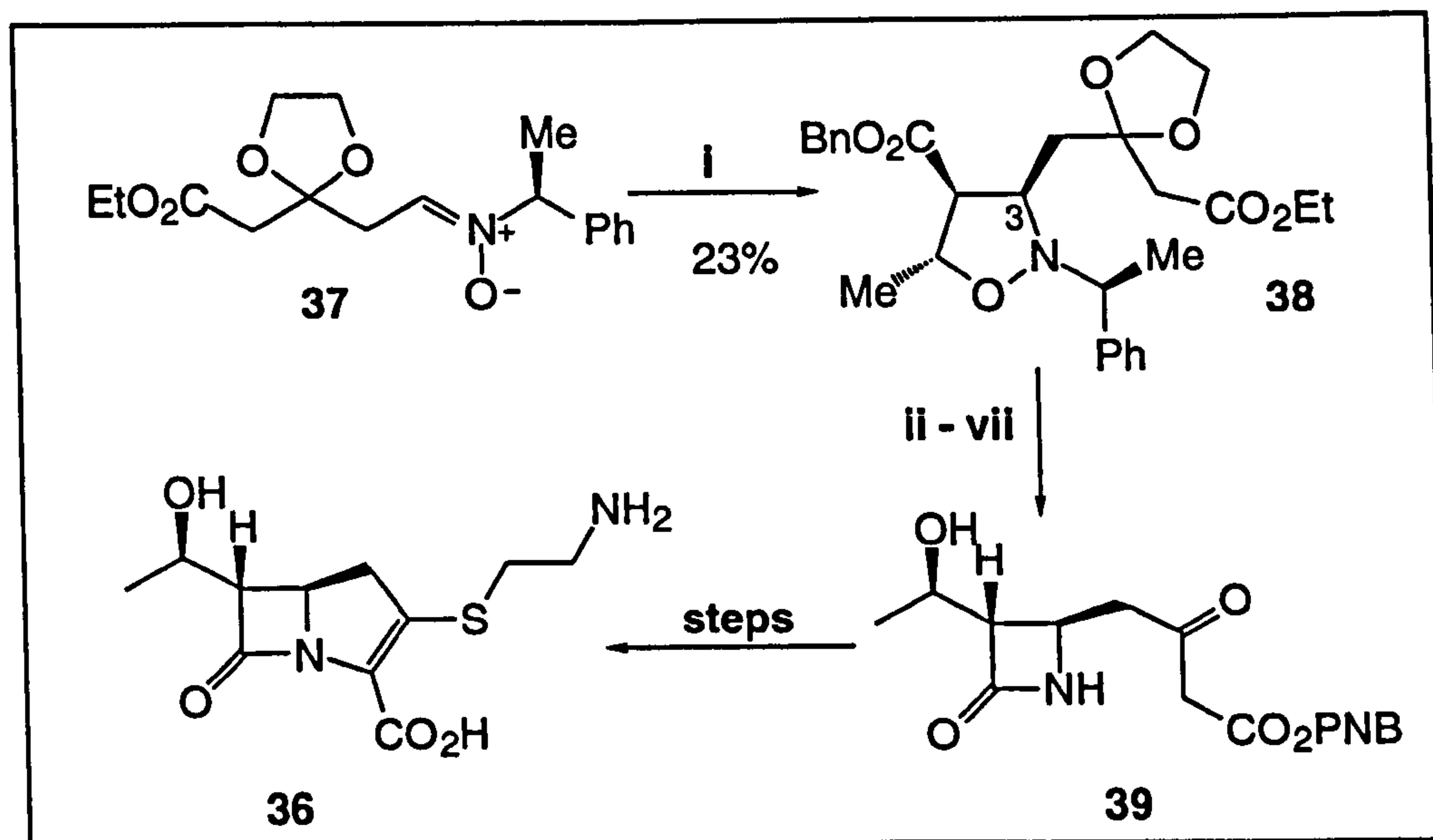


Reagents : i, $\text{CH}_2=\text{CHCH}_2\text{OH}$, C_6H_6 , Δ , 3h; ii, $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -70°C ; iii, 3Å mol. sieves, C_6H_6 ; iv, NaBH_4 , $\text{H}_2\text{N}(\text{CH}_2)_4\text{CH}(\text{CO}_2\text{Bn})\text{NHCbz}$, MeOH, 5°C ; v, H_2 , Pd-C, HCl, EtOH.

Scheme 21

Overton has applied the 1,3-dipolar cycloaddition of N-(1-phenylethyl)nitrones to the synthesis of a number of amino-acids, including (*R*)- and (*S*)-lysine,^{73,74} as well as aspartame and its (*R*)-aspartyl isomer.⁷⁵ Kametani used related nitrones in the synthesis of precursors to (+)-thienamycin **36** and its (-)-isomer, as well as to penems and carbapenems.^{66,76,77} The reaction of nitron **37** with benzyl crotonate gave a 1:1 mixture of the desired (3*S*)-isoxazolidine **38** and its (3*R*)-isomer (Scheme 22). Hydrogenolysis of

38 was followed by DCC coupling to generate the azetidinone moiety. After TBDMS-protection of both the hydroxy and lactam functionalities, the ethyl ester was hydrolysed for conversion to the *p*-nitrobenzyl ester to afford the known (+)-thienamycin intermediate **39**. In this fashion, the (3*R*)-isomer of **38** was used to prepare the analogous intermediate to (-)-thienamycin.⁷⁶



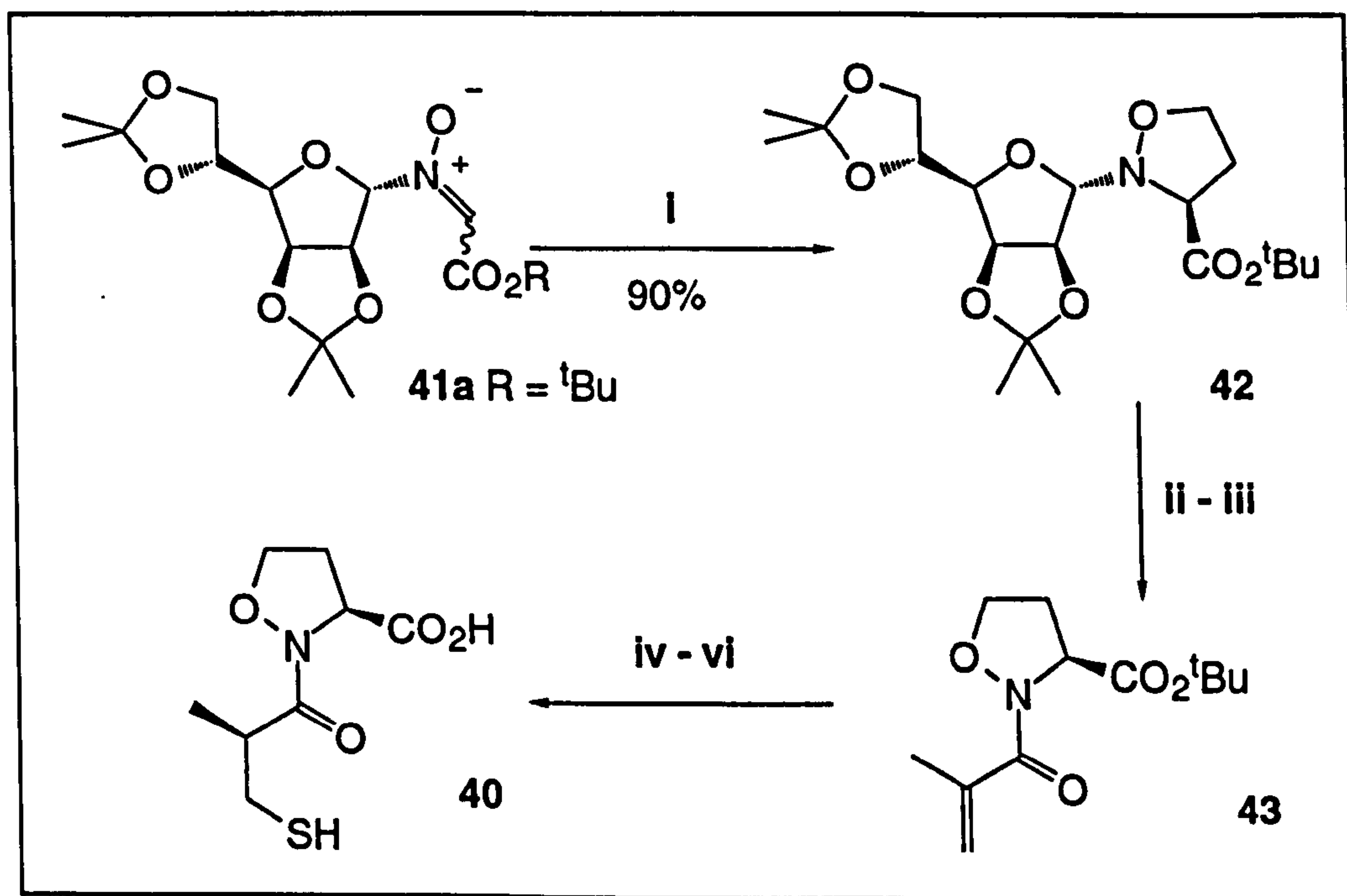
Reagents : i, $\text{MeCH=CHCO}_2\text{Bn}$, C_6H_6 , Δ , 16h; ii, H_2 , 10% Pd-C, AcOH, 38h; iii, DCC, MeCN, 60°C , 3h; iv, TBDMSCl, Et_3N , DMF; v, 0.25M aq. NaOH, H_2O , THF; vi, *p*-NO₂-BnBr, DMF, 2h; vii, c. HCl, MeOH.

Scheme 22

Although cheap and readily available, in general, these N-(1-phenyl)ethylnitrones are, as reported by Belzecki, of limited use in asymmetric 1,3-dipolar cycloaddition reactions.^{70,71} This is due to poor discrimination resulting from the free rotation about the N-to-auxiliary bond, leading to a mixture of diastereoisomers.

The use of glycosides as the chiral group on the nitron nitrogen atom was pioneered by Vasella and has been used in the asymmetric synthesis of a number of biologically

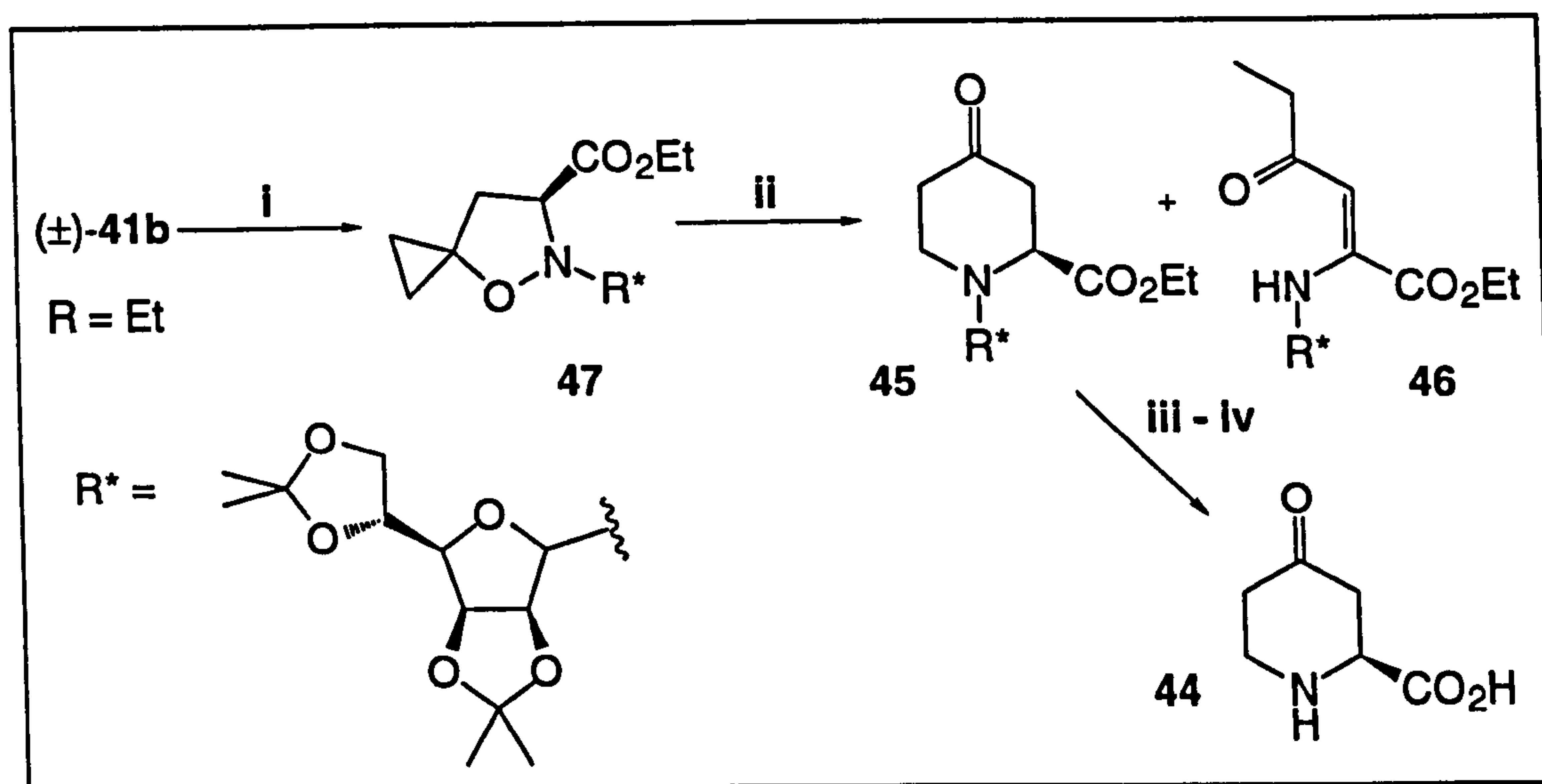
important molecules or their analogues including proline,^{78,79} nucleosides⁸⁰ and (+)-nojirimycin and its 1-deoxy-analogue.⁸¹ For example, the captopril analogue **40** was prepared, in which the proline of the natural material has been replaced by the 5-oxaproline moiety (Scheme 23).⁷⁹ The optically active N-glycosylnitrone **41a** underwent a 1,3-dipolar cycloaddition with ethene at 65 atmos. in 90% yield to give predominantly the desired isoxazolidine isomer **42**. Cleavage of the glycoside was followed by treatment with methacryloyl chloride to afford the amide **43**. Conjugate addition of thioacetic acid gave a 1:1 mixture of the diastereoisomers, which could be separated by chromatography. Hydrolysis of the *tert*-butyl ester with TFA and aminolysis of the thioester with concentrated ammonia, afforded the target compound **40**. One distinct advantage of the glycoside auxiliaries developed by Vasella and co-workers is their recovery after acid hydrolysis from the isoxazolidine cycloadduct.



Reagents : i, CH₂=CH₂, 65 atmos., 80°C; ii, aq. HCl, 6h; iii, methacryloyl chloride, pyridine, -10°C, 2h; iv, CH₃COSH, 0°C, 15min; v, TFA, 1-chlorobutane, 25°C, 2h; vi, c. aq. NH₃, 25°C, 24h.

Scheme 23

Brandi has applied a similar glycosyl nitron (\pm)-**41b** to the synthesis of the unusual amino-acid (2*S*)-4-oxopiperic acid **44** (Scheme 24).⁸² The tetrahydropyridin-4-one **45** was obtained, along with the open chain by-product **46**, *via* thermal rearrangement of the spirocyclic isoxazolidine cycloadduct **47**. The chiral auxiliary (R^*) was recovered after its removal from **45** with TFA, and hydrolysis of the amino ester with 6M aqueous HCl afforded the amino-acid **44**.

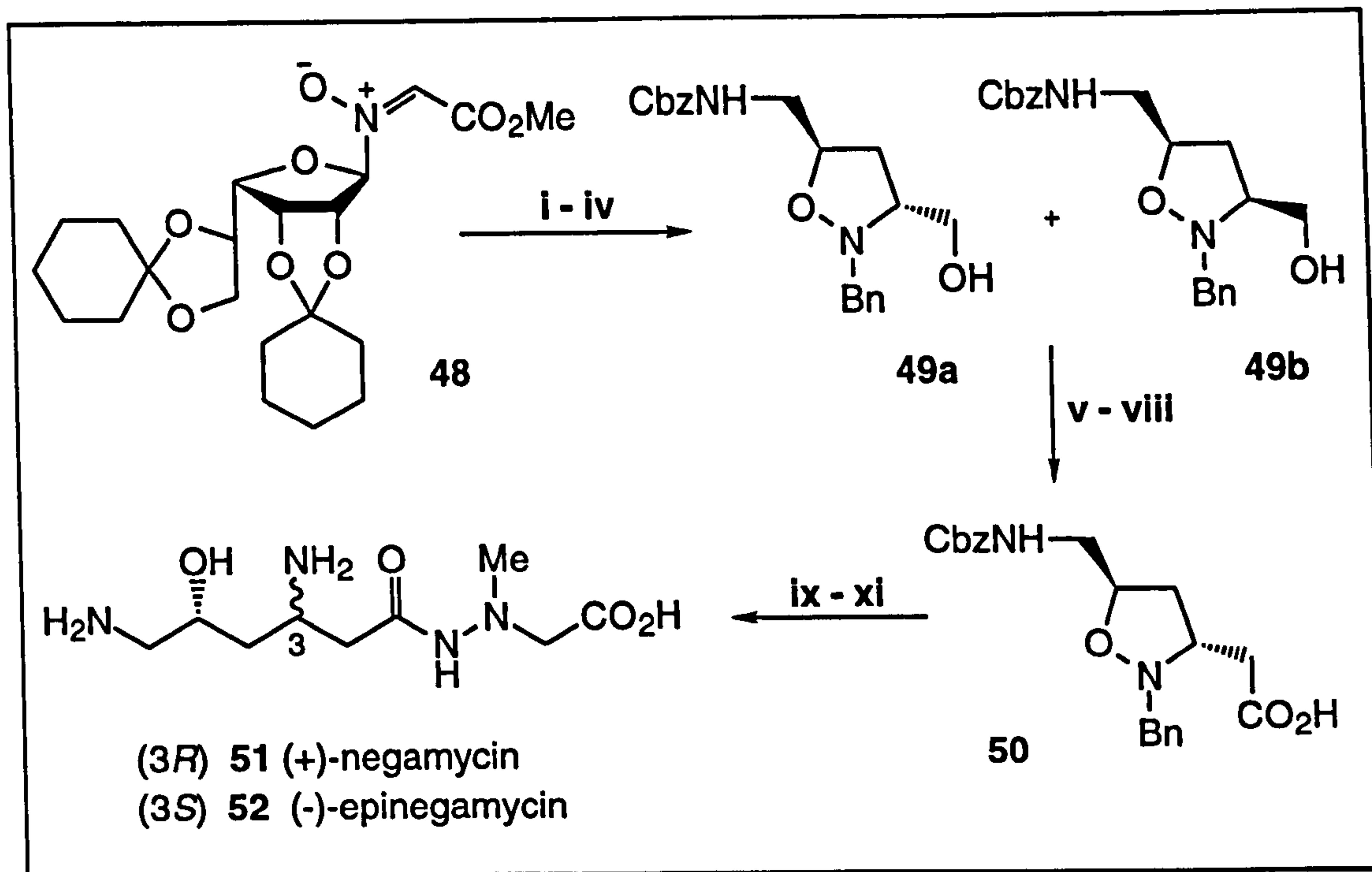


Reagents : i, methylenecyclopropane, toluene, 60°C, 5 days; ii, xylenes, 140°C; iii, TFA, EtOH; iv, 6M aq. HCl.

Scheme 24

A number of carbohydrate-derived nitrones have been prepared by Kibayashi.^{83,84} The gulofuranose nitron **48** exists as a mixture of *E*- and *Z*- isomers, and led to a mixture of two diastereomeric isoxazolidines in the 1,3-dipolar cycloaddition to Cbz-protected allylamine (Scheme 25). The diastereomers were separated, and the auxiliary removed, to yield the optically pure isoxazolidines **49a** and **49b**. Adduct **49a** was converted into the nitrile and thence to the acid **50** in order to facilitate formation of the hydrazide moiety. The

Cbz-group was removed by catalytic hydrogenolysis, and simultaneous N-O cleavage afforded (+)-negamycin **51**. Similarly, the isoxazolidine **49b** was manipulated to afford the (3*S*)-epimer of this natural product, (-)-epinegamycin **51**.



Reagents : i, CH₂=CHCH₂NHCbz; ii, 10% aq. HCl; iii, BnBr iv, LiAlH₄; v, TsCl, ⁱPrNEt, Et₃N;
 vi, NaCN, DMSO; vii, HCl/EtOH; viii, 4% aq. NaOH, MeOH; ix, ClCO₂Et, Et₃N, toluene;
 x, benzyl (1-methylhydrazino)acetate; xi, H₂, 3 atm., Pd-C, 10% aq. AcOH, MeOH.

Scheme 25

One problem that has regularly reduced the potential for asymmetric induction of many of the nitrones discussed thus far is the free rotation of the C- or N-to-auxiliary bond. Many researchers have found that the auxiliary is of little use if it is free to rotate in the transition state of the 1,3-dipolar cycloaddition reaction. The use of chiral cyclic nitrones confers a much more rigid conformation on the nitron and allows highly effective shielding of the chosen face of the nitron by the chiral substituent in the ring. In addition, cyclic

nitrones are unable to interconvert between the *E*- and *Z*-isomers of the nitronone, so this extra stereochemical complication is absent. Vasella was one of the first to take advantage of the improved facial selectivity in 1,3-dipolar cycloaddition reactions offered by cyclic nitrones. His sugar-derived spirocyclic nitronone **53**⁸⁵ was followed by many others including the range of tartaric-acid-derived nitrones such as **54a** and **54b**^{58,86-89}, or **55** derived from erythritol,^{90,91} **56** from malic acid,^{92,93} or **57** from prolinol (Figure 13).⁹⁴

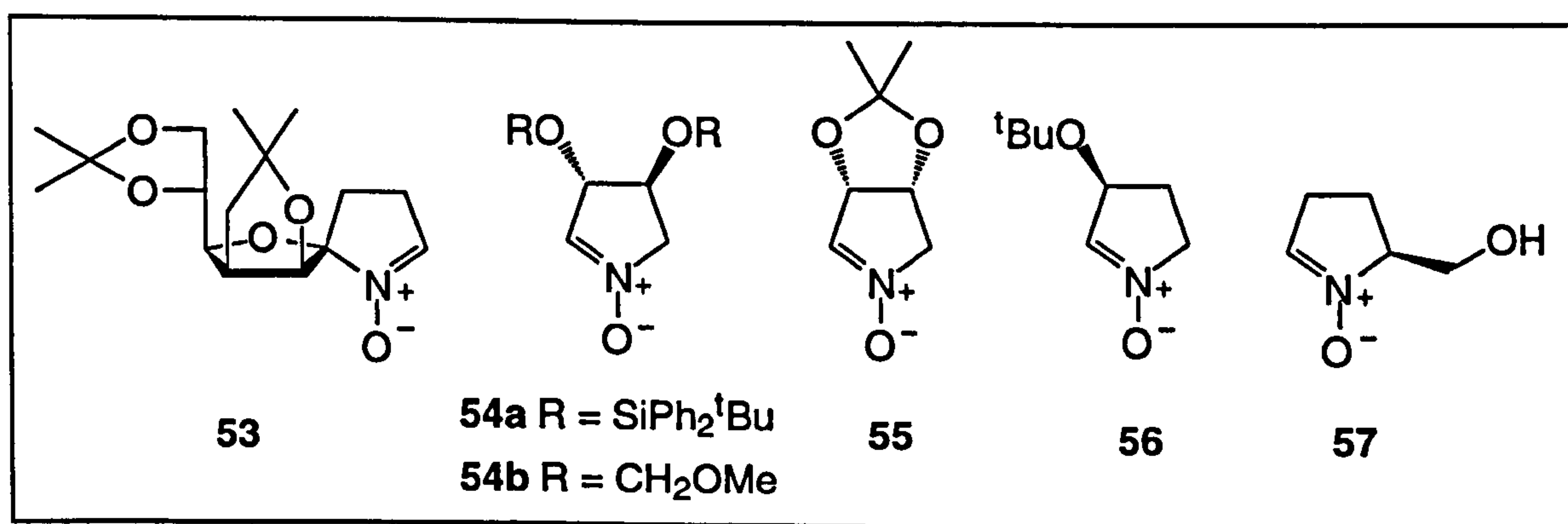
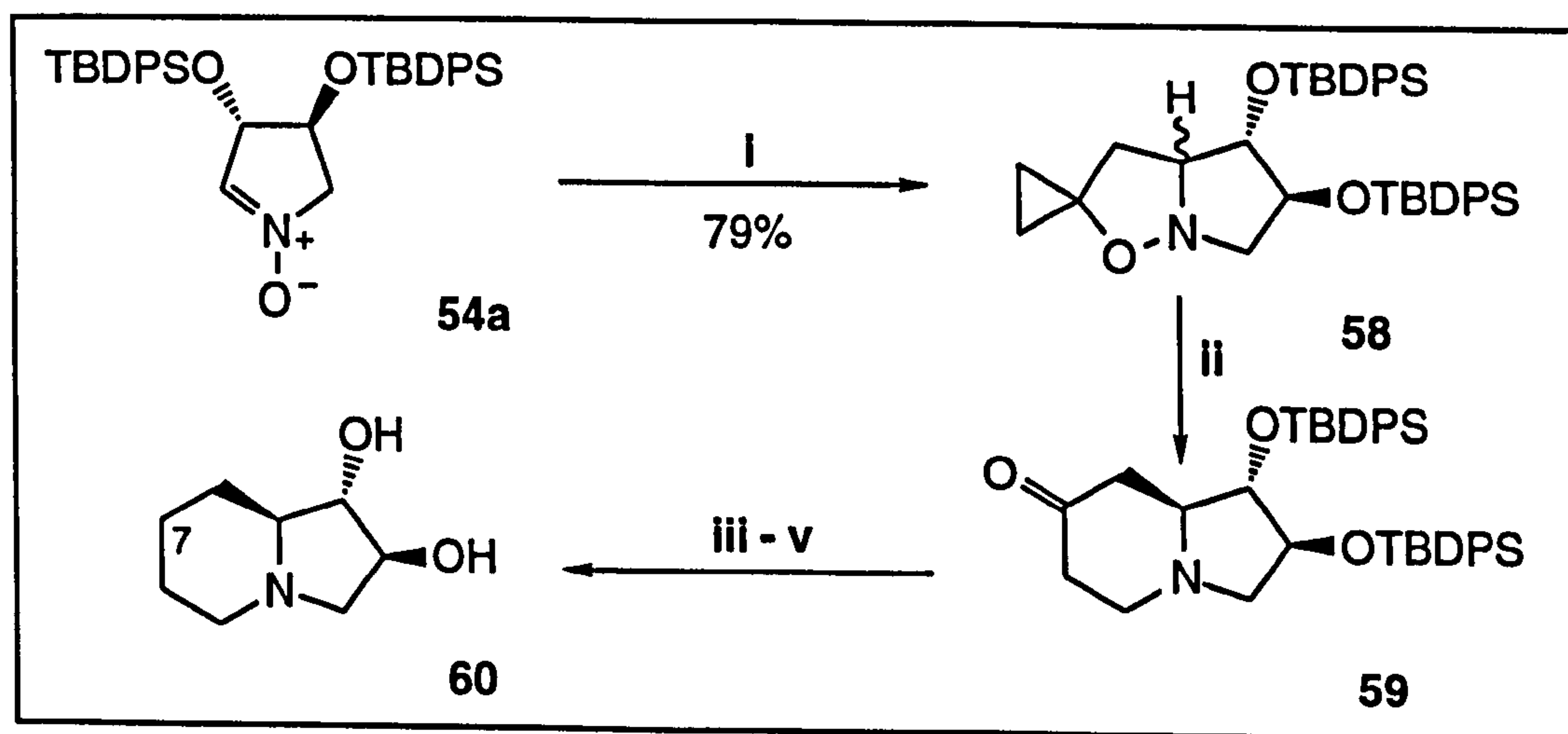


Figure 13



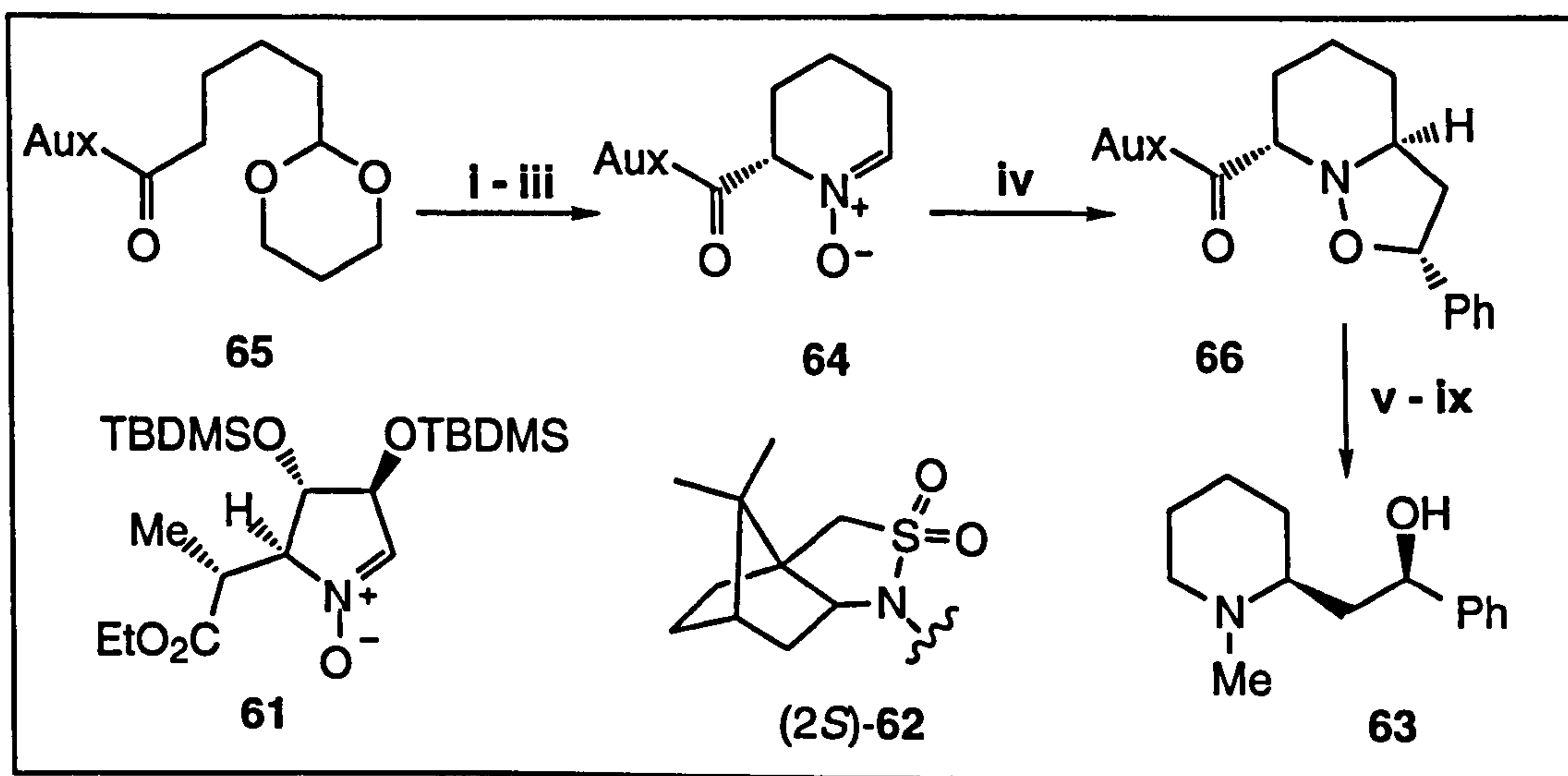
Reagents : **i**, methylenecyclopropane, C₆H₆, 7 days, 25°C; **ii**, xylenes, 140°C, 1.5h; **iii**, TsNHNH₂, MeOH, 7h; **iv**, NaBH₄, 65°C, 20h; **v**, 40% aq. HF, CH₃CN, 25°C, 2 days.

Scheme 26

Brandi has used these reagents in the synthesis of a number of indolizidines,^{86-88,92} also utilising the 5-aza-4-oxaspiro[2,4]heptane to piperidin-4-one rearrangement seen in his route to (2*S*)-4-oxopiperic acid **44** (Scheme 24).⁸² For example, the L-tartrate-derived nitron **54a** gave the desired regioisomer of the spiro-isoxazolidine cycloadduct **58** as a 10:1 mixture of the separable diastereoisomers (Scheme 26). The desired isomer was thermally rearranged to the intermediate ketone **59**. The target indolizidine alkaloid lentiginosine **60** was then obtained by decarbonylation and removal of the silyl protecting groups. The bicyclic ketone **59** was also used to prepare both of the C-7 hydroxylated epimers of this target molecule.^{86,87} Brandi has employed a similar strategy with the malic acid-derived nitron **56**, to synthesise further indolizidines.⁹²

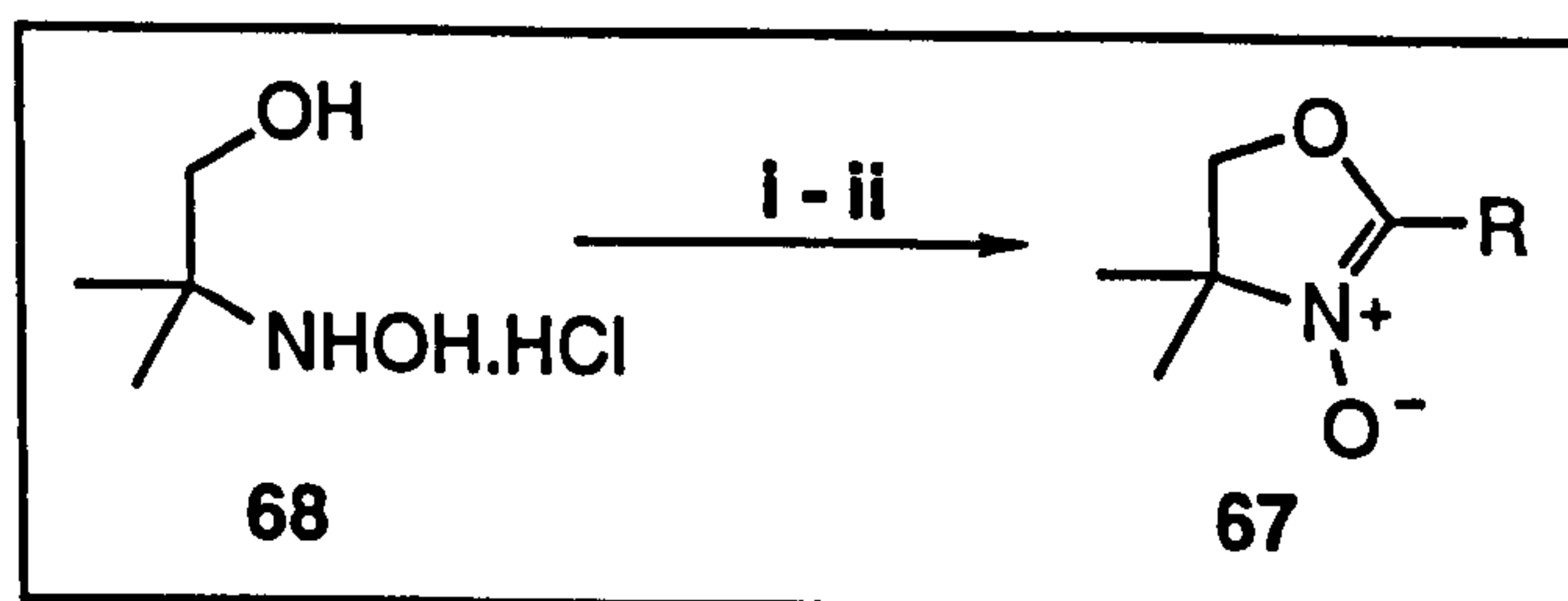
Wightman *et al.* have developed nitron **55** derived from erythritol for cycloaddition with a silyl-protected allyl alcohol to prepare homochiral polyhydroxylated pyrrolizidines and indolizidines.^{90,91} The L-(+)-prolinol-derived nitron of de March *et al.* **57** gave complete diastereofacial selectivity in its cycloaddition reactions with a number of different dipolarophiles, but *endo:exo* selectivities were variable.⁹⁴ The homochiral nitron **61** (Scheme 27) developed by Saito *et al.* combines features from nitrones **54** and **57** and its cycloadditions with fumaric and maleic acid derivatives proceed with complete regio- and diastereoselectivity.⁹⁵ Oppolzer *et al.* have used a nitron carrying their well-known (2*S*)-bornane-10,2-sultam chiral auxiliary **62**^{96,97} in the total synthesis of (-)-allosedamine **63**.⁹⁸ The homochiral nitron **64**, produced from an acyclic starting material **65**, underwent a 1,3-dipolar cycloaddition with styrene to produce only the *exo* isomer of isoxazolidine **66** with a *de_{exo}* of 93%. The sultam auxiliary was removed with lithium hydroxide, and recovered in almost quantitative yield, whilst the resultant carboxylate side-chain was

converted to the nitrile. N-Methylation with methyl triflate was followed by N-O bond cleavage and decyanation with zinc in acetic acid to afford the natural product **63**.



Reagents : i, $\text{NaN}(\text{SiMe}_3)_2$, THF, -78°C , 1h; ii, 1-chloro-1-nitrosocyclohexane, -78°C , 1h; iii, 2M aq. HCl, -78°C , 12h; iv, styrene, CH_2Cl_2 , Δ , 2h; v, LiOH, THF, 55°C , 30h; vi, $i\text{BuOCOC}\text{Cl}$, N-methylmorpholine, -15°C then gaseous NH_3 , 25°C ; vii, $(\text{CF}_3\text{CO})_2\text{O}$, 1,4-dioxane, pyridine, 25°C , 1h; viii, $\text{MeOSO}_2\text{CF}_3$, CH_2Cl_2 , -10°C , 20min, $\rightarrow 25^\circ\text{C}$, 30min.; ix, Zn dust, H_2O , THF, 2M aq. HCl, AcOH, 25°C , 20h.

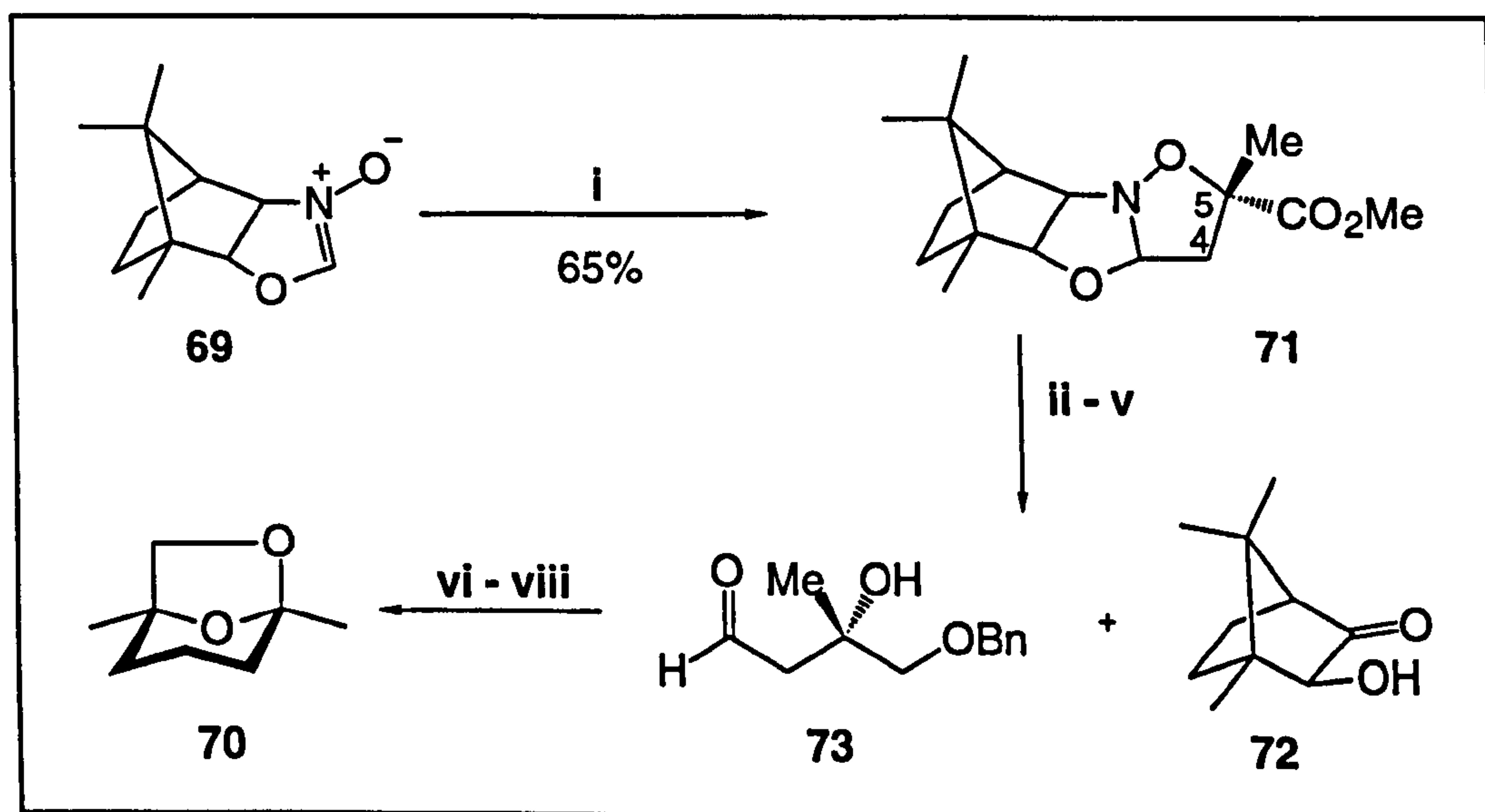
Scheme 27



Reagents : i, $\text{RC}(\text{OEt})_3$, CH_2Cl_2 , 25°C , 1h; ii, Et_3N .

Scheme 28

The synthesis of oxazoline nitrones **67** from the β -hydroxylaminoalcohols **68**, originally devised by Coates and Ashburn (Scheme 28),^{99,100} has been extended by Langlois *et al.* to produce the camphor-derived nitron **69** for the total synthesis of (-)-frontalin **70** (Scheme 29).¹⁰¹ The 1,3-dipolar cycloaddition of the nitron **69** with methyl methacrylate produces the *endo* isomer of the 5-isoxazolidine **71** as the major product (*endo:exo* >95:5, 5-substituted:4-substituted >95:5). The methyl ester of this cycloadduct is reduced to the alcohol and protected as the benzyl ether before isoxazolidine N–O cleavage, and removal and recovery of the camphor auxiliary **72** to give the aldehyde **73**. This compound is a known intermediate in the synthesis of (-)-frontalin **70**, and is converted to the natural pheromone in two steps.



Reagents : **i**, methyl methacrylate, toluene, 80°C, 2h; **ii**, LiAlH₄, Et₂O, 0.5h; **iii**, BnBr, cat. *n*-Bu₄I, THF/DMF, 0 → 25°C, 4h; **iv**, *m*CPBA, Et₂O, 25°C, 1h; **v**, 2M aq. HCl, THF, 25°C, 5mins.; **vi**, Ph₃P=CHCOCH₃, MeCN, Δ, 4h **vii** H₂, Pd-C, MeOH, 18h.

Scheme 29

The Langlois group has also used this methodology in the synthesis of β -lactones¹⁰² and the potential AIDS treatment (+)-carbovir.¹⁰³ In this latter example, the 1,3-dipolar cycloaddition of nitron 69 with cyclopentadiene proceeds at 40°C with high regio- and stereoselectivity and, as in the frontaline synthesis, the camphor skeleton 72 is recovered.

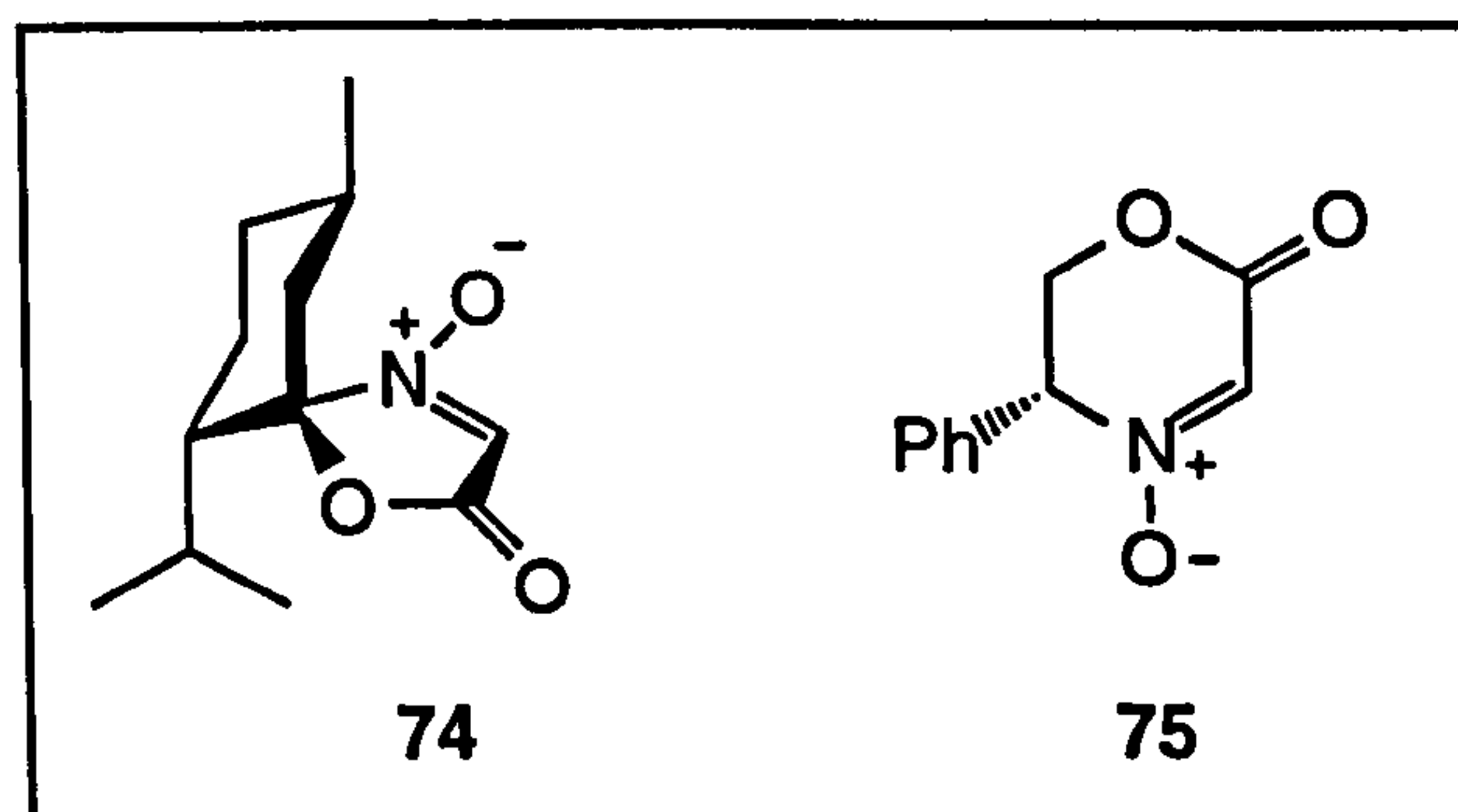
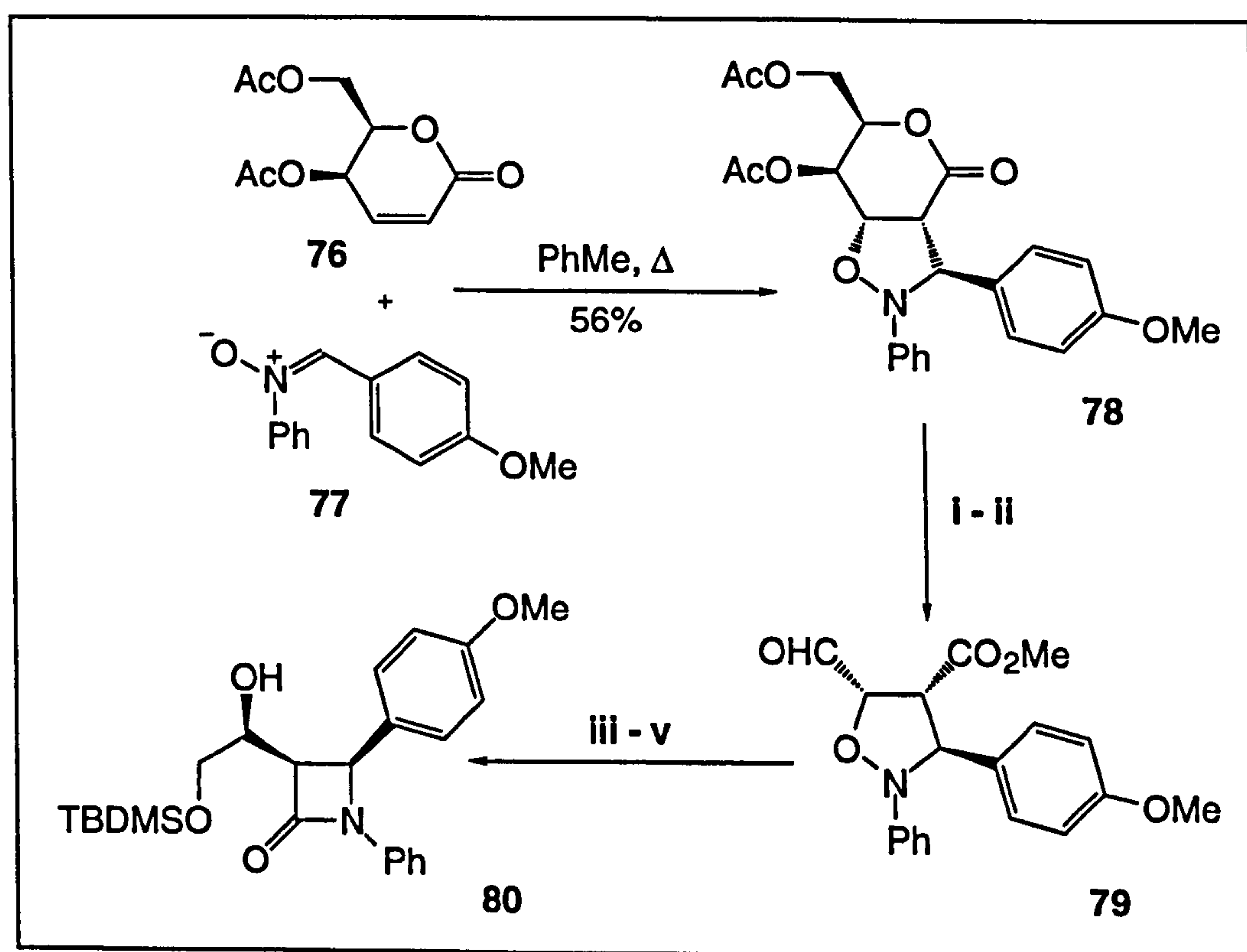


Figure 14

The L-menthone-derived nitron 74 was produced by Katagiri *et al.*, and gave a single isoxazolidine product in 90% yield in its 1,3-dipolar cycloaddition reaction with allyltrimethylsilane at 40°C and 800MPa (Figure 14).^{104,105} This cycloadduct was manipulated to yield enantiomerically pure amino-acids *via* methodology that allowed regeneration of the L-menthone auxiliary. The morpholinone nitron 75 was prepared by Tamura *et al.* for reaction with a number of alkene dipolarophiles: the reaction with 2-methylpropene gives an 87% yield of a single isomer of the isoxazolidine cycloadduct.^{106,107}

1.3.2 Chiral alkene dipolarophiles in 1,3-dipolar cycloadditions

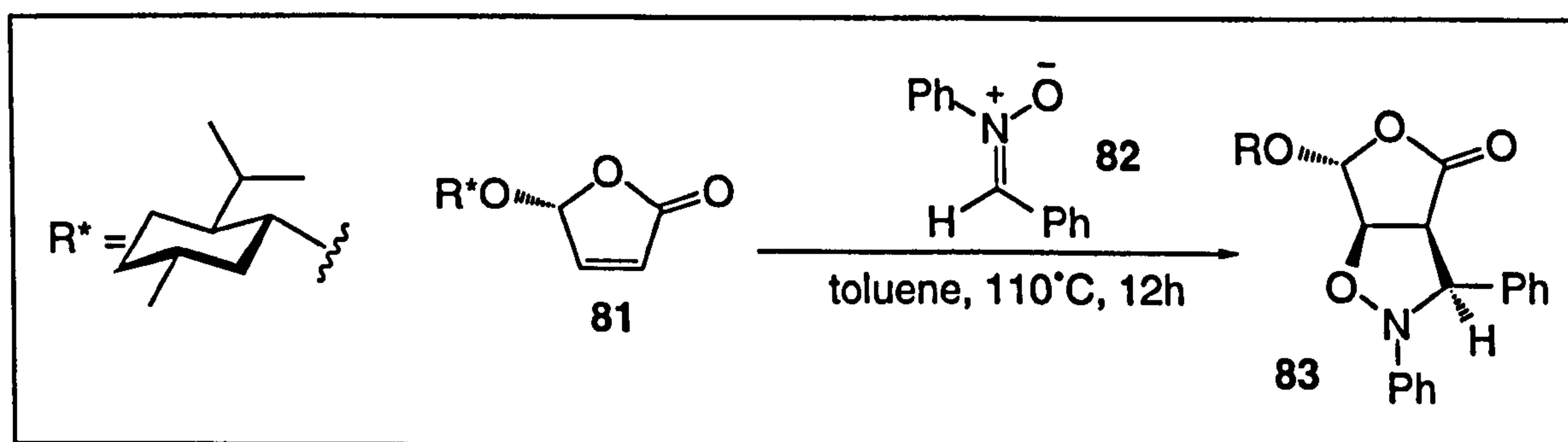
The first chiral alkenes to be employed in nitron 1,3-dipolar cycloaddition reactions were unsaturated natural products and related compounds, including lumisantonin, the steroid skeleton¹⁰⁸ and elaiophylin.¹⁰⁹ Subsequent work has focussed mainly on the utility of chiral α,β -unsaturated carbonyl compounds (especially lactones,¹¹⁰⁻¹¹⁷ esters¹¹⁸⁻¹²¹ and amides¹²²), vinylic and allylic ethers,¹²³⁻¹²⁸ allylic amines,¹²⁹⁻¹³⁴ as well as vinylic sulphoxides^{55,57,135-138} and phosphine oxides.^{55-60,139}



Reagents : i, NaOMe, MeOH, 20°C, 15min; ii, NaIO₄, MeOH, H₂O, 20°C, 24h; iii, NaCNBH₃, 2M aq. HCl, MeOH, 20°C, 1h; iv, TBDMSCl, imidazole, DMF, 20°C; v, H₂, 10% Pd-C, MeOH, 20°C.

Scheme 30

The use of chiral α,β -unsaturated lactone dipolarophiles derived from sugars has been studied vigorously by a number of groups, and Chmielewski *et al.* were able to apply this cycloaddition approach to the synthesis of chiral β -lactams.^{110,112} The chiral dehydrolactone **76** reacted regio-, stereo- and facioselectively with C-(4-methoxyphenyl)-N-phenylnitrone **77**, to give the bicyclic isoxazolidine **78** in 56% yield (Scheme 30). The acetate protecting groups and the lactone were methanolysed to afford a monocyclic triol, from which a two-carbon segment was excised by vicinal diol cleavage with sodium periodate. This afforded the aldehyde **79**, which was reduced with sodium cyanoborohydride, and the resultant alcohol protected as its TBDMS ether. Hydrogenolysis of the isoxazolidine N-O bond allowed spontaneous ring-closure to afford the β -lactam **80** in 60% overall yield. In a related report, Paton *et al.* have shown that the 1,3-dipolar cycloaddition reaction between the cellulose-derived bicyclic lactone levoglucosenone and C,N-diphenylnitrone, give a single diastereomer of the cycloadduct (68%) although reaction is slow (two days at 110°C).^{113,114}

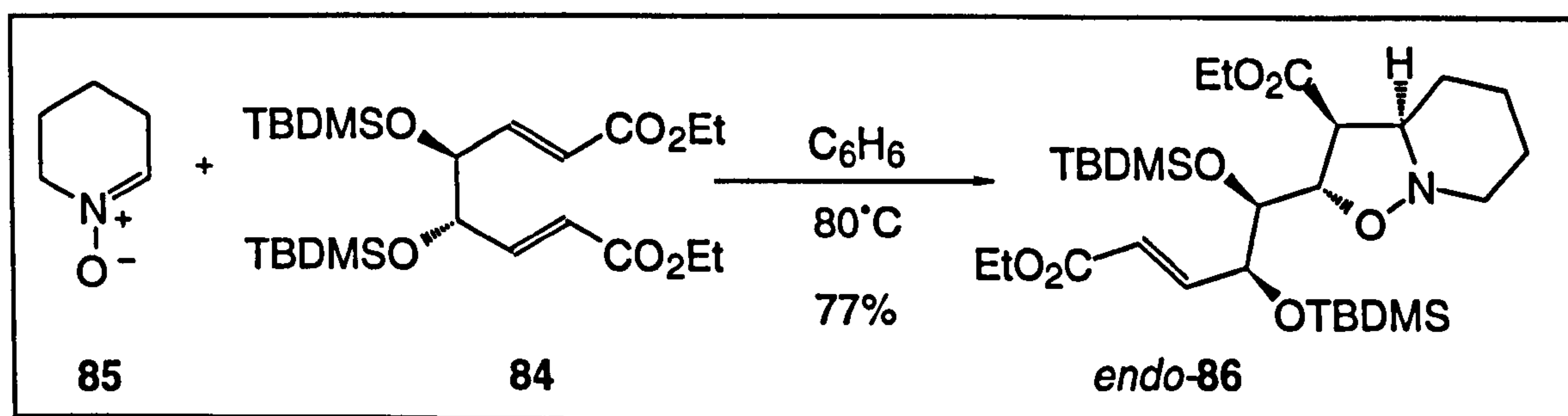


Scheme 31

Feringa *et al.* have carried out a number of nitrone cycloadditions with chiral furanone dipolarophiles.^{116,117} They prepared the chiral 4-substituted furanone **81** from the racemic 4-hydroxyfuranone and menthol, by epimerisation of the unwanted diastereomer

and simultaneous crystallisation of **81** from the reaction mixture. Subsequent reaction with C,N-diphenylnitrone **82** affords the *exo* isoxazolidine **83** along with the *endo* isomer (80% yield, *exo:endo* = 65:35) (Scheme 31). The diastereofacial selectivity of the cycloaddition is due to the highly effective shielding of one face of the alkene by the menthol moiety (R*). A similar strategy has been used in the synthesis of bicyclo[3.3.0]isoxazolidinyl nucleosides in the discovery of novel anti-HIV agents.¹¹⁵

An example of the use of chiral, acyclic α,β -unsaturated ester dipolarophiles is provided by Saito *et al.*, who have employed a range of tartaric acid derivatives in nitrone cycloadditions.¹⁴⁰ Reaction between **84** and 2,3,4,5-tetrahydropyridine-N-oxide **85** gives almost exclusively *endo*-**86**, with excellent diastereofacial selectivity (>98%) (Scheme 32). Other nitrones, both cyclic and acyclic, were used in 1,3-dipolar cycloaddition reactions with this alkene and they showed moderate to excellent *endo:exo* selectivities and excellent diastereofacial selectivity. 1,3-Dipolar cycloaddition reactions with γ -hydroxy- α,β -unsaturated carbonyl compounds have been investigated by other research groups^{119,141,142} but all show lower selectivities than those of Saito *et al.*



Scheme 32

There has been a small number of investigations which have used vinyl ester dipolarophiles carrying the chiral auxiliary on the carboxylate. The esters **87** developed by

Tejero¹⁴³ and **88** by Carriere¹⁴⁴ showed very poor selectivities, in contrast to the camphor-derived vinyl ester **89** of Olssen,¹⁴⁵ which demonstrated excellent diastereofacial selectivity but no *endo:exo* selectivity (Figure 15).

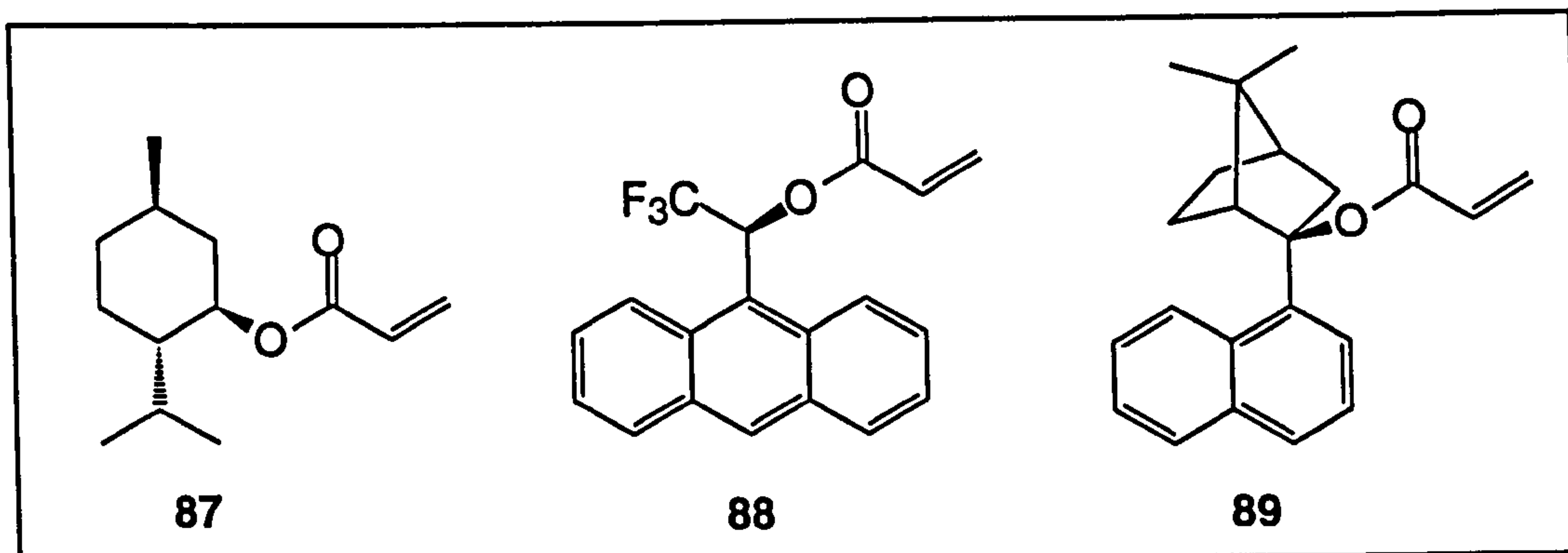
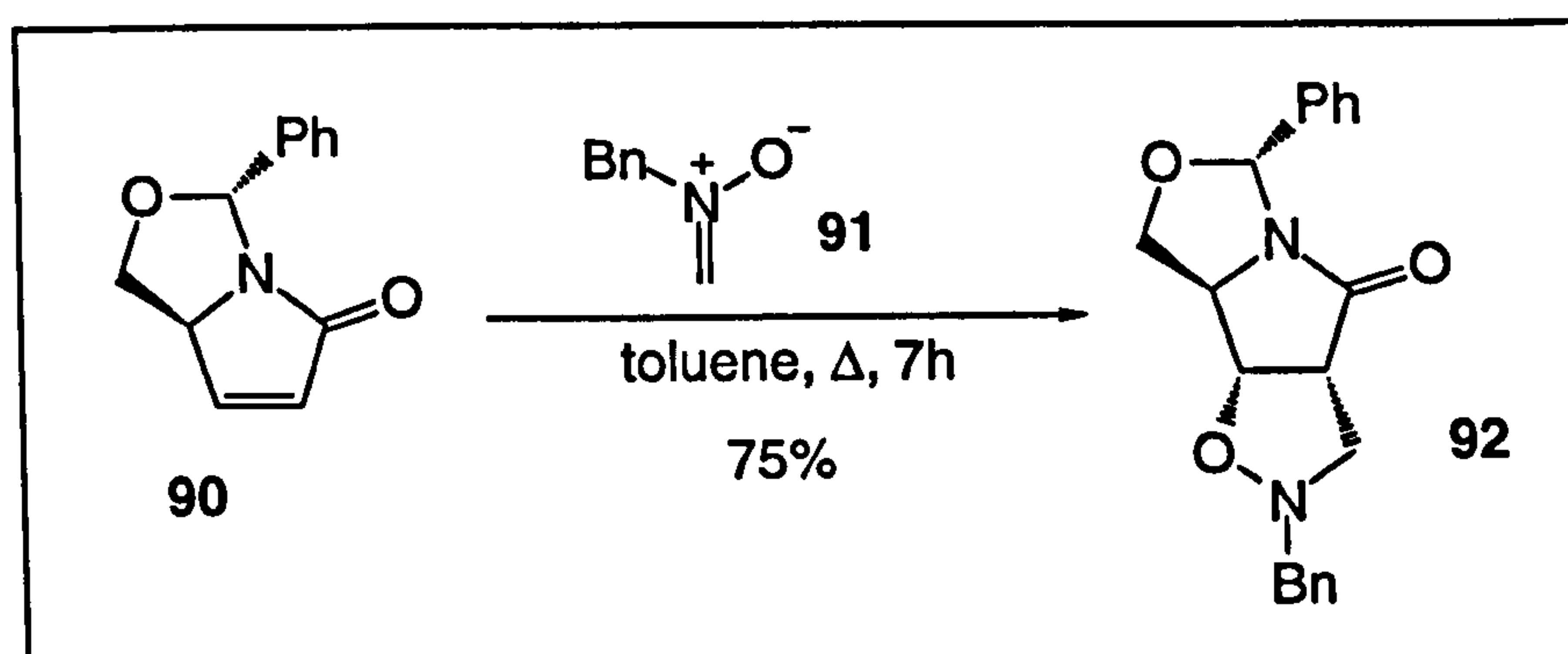


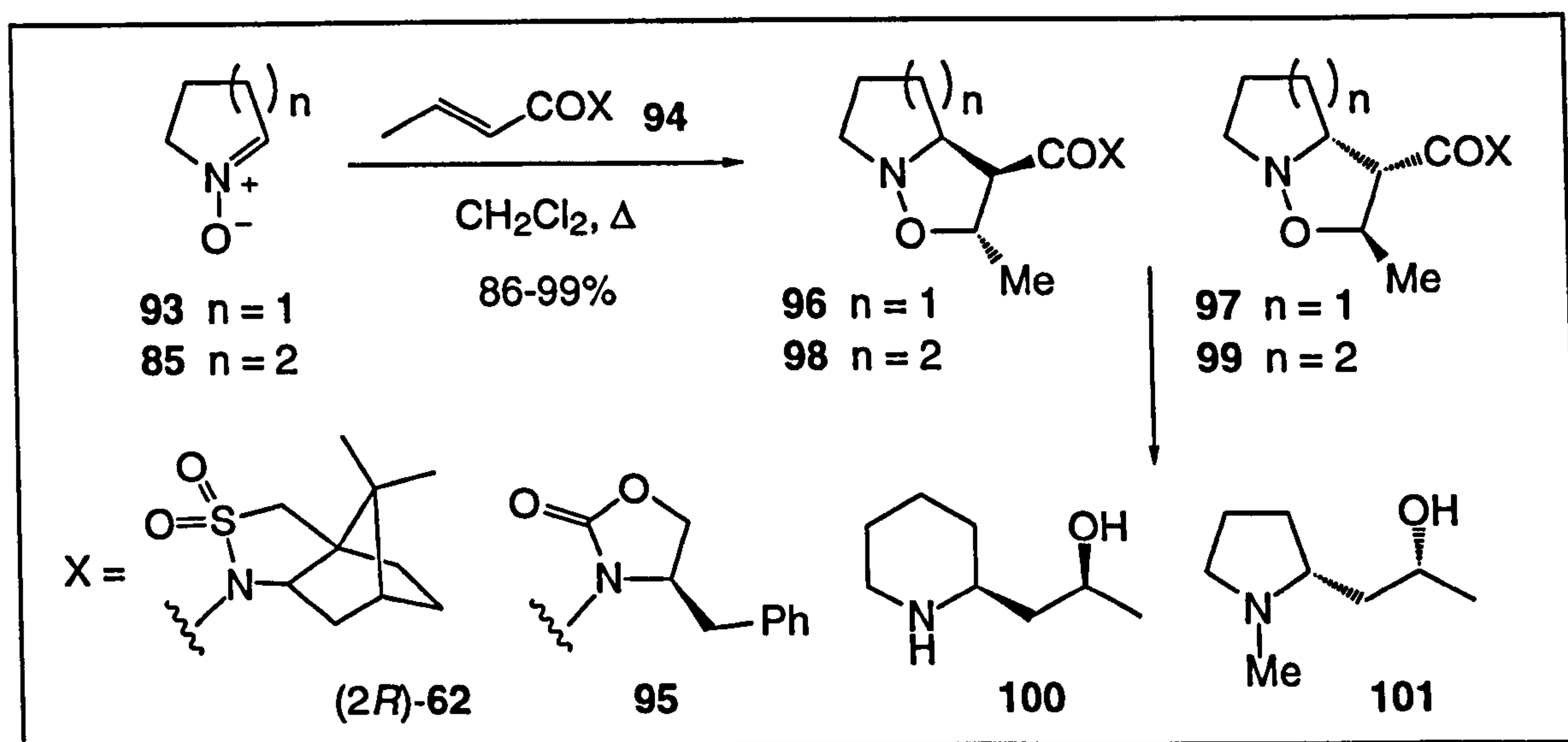
Figure 15



Scheme 33

N. Langlois *et al.* have applied chiral α,β -unsaturated γ -lactams such as **90** derived from (*S*)-pyroglutaminol in reactions with N-benzyl nitron **91** (Scheme 33).¹⁴⁶ They observed a 75% yield of tricyclic isoxazolidine **92** and only 3% and 5% of two other isomers as well as 4% of the product of 1,4-addition of N-benzylhydroxylamine. Murahashi *et al.* have utilised chiral α,β -unsaturated amides to prepare isoxazolidine precursors to enantiopure natural products (Scheme 34).¹²² The cyclic nitrones **93** and **85** were reacted with crotonamide dipolarophiles **94** containing either the (2*R*)-enantiomer of Oppolzer's

sultam moiety (2*R*)-**62** or (*R*)-4-benzyl-2-oxazolidinone **95** as the chiral auxiliary, to afford excellent yields of the *endo* cycloadducts **96/97** and **98/99**. The sultam of isoxazolidine **98** was further manipulated to afford (+)-sedridine **100** after hydrolysis, Barton decarboxylation and hydrogenolysis. The related natural product (+)-hygroline **101** was prepared from the sultam of isoxazolidine **97** by a similar procedure, which included N-methylation prior to N–O bond hydrogenolysis.

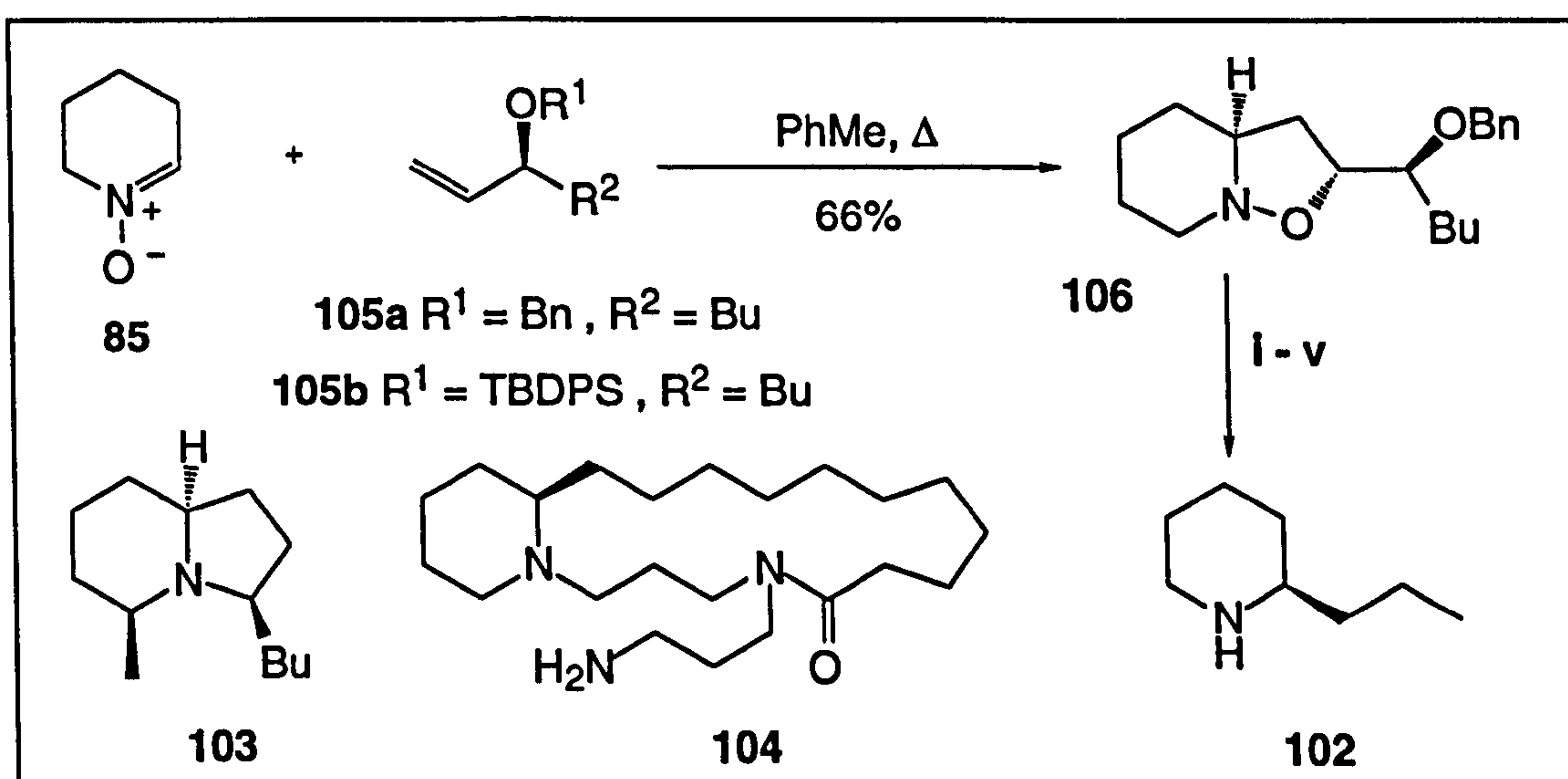


Reagents : (X= (2*R*)-**62** : **98**→**100**) i, aq. LiOH ii $t\text{BuOCOC}\text{Cl}$, N-methyl-morpholine; iii, 2-mercaptopyridine-N-oxide, Et_3N ; iv, $t\text{BuSH}$, $h\nu$; v, H_2 , Pd-C; (X=**95** : **97**→**101**) i to iv, above; v, CH_3I ; vi, H_2 , Pd-C.

Scheme 34

Chiral vinyl ethers have generated little research interest in the field of asymmetric nitron cycloadditions, although most notably these dipolarophiles have been used by Carruthers *et al.* to prepare enantiopure piperidine alkaloids,¹²³ and by De Shong *et al.* in the synthesis of the amino-sugar daunosamine.⁶² By contrast, the use of chiral allylic ethers and alcohols is extensive and well illustrated in the work of Kibayashi *et al.* who

championed this approach and demonstrated its worth by the total synthesis of a number of natural products including (-)-coniine **102**,¹²⁶ (+)-monomorine I **103**,^{124,125} and (-)-oncinotine **104** (Scheme 35).¹²⁷ The O-benzylallylic ether **105a** was reacted with 2,3,4,5-tetrahydropyridine-N-oxide **85** to afford a 4:1 mixture of isoxazolidine cycloadducts from which the major isomer **106** was isolated to provide (-)-coniine **102** in a further five steps. The cycloadduct of **85** and a silylated allylic ether **105b** was manipulated to afford the macrocyclic spermidine alkaloid (-)-oncinotine **104**. The indolizidine (+)-monomorine I **103** was also prepared from allylic ether **105a** by cycloaddition to a glyoxalate-derived nitron, followed by a lengthy elaboration. A number of other workers have carried out related investigations with chiral allylic ether dipolarophiles.^{147,148}



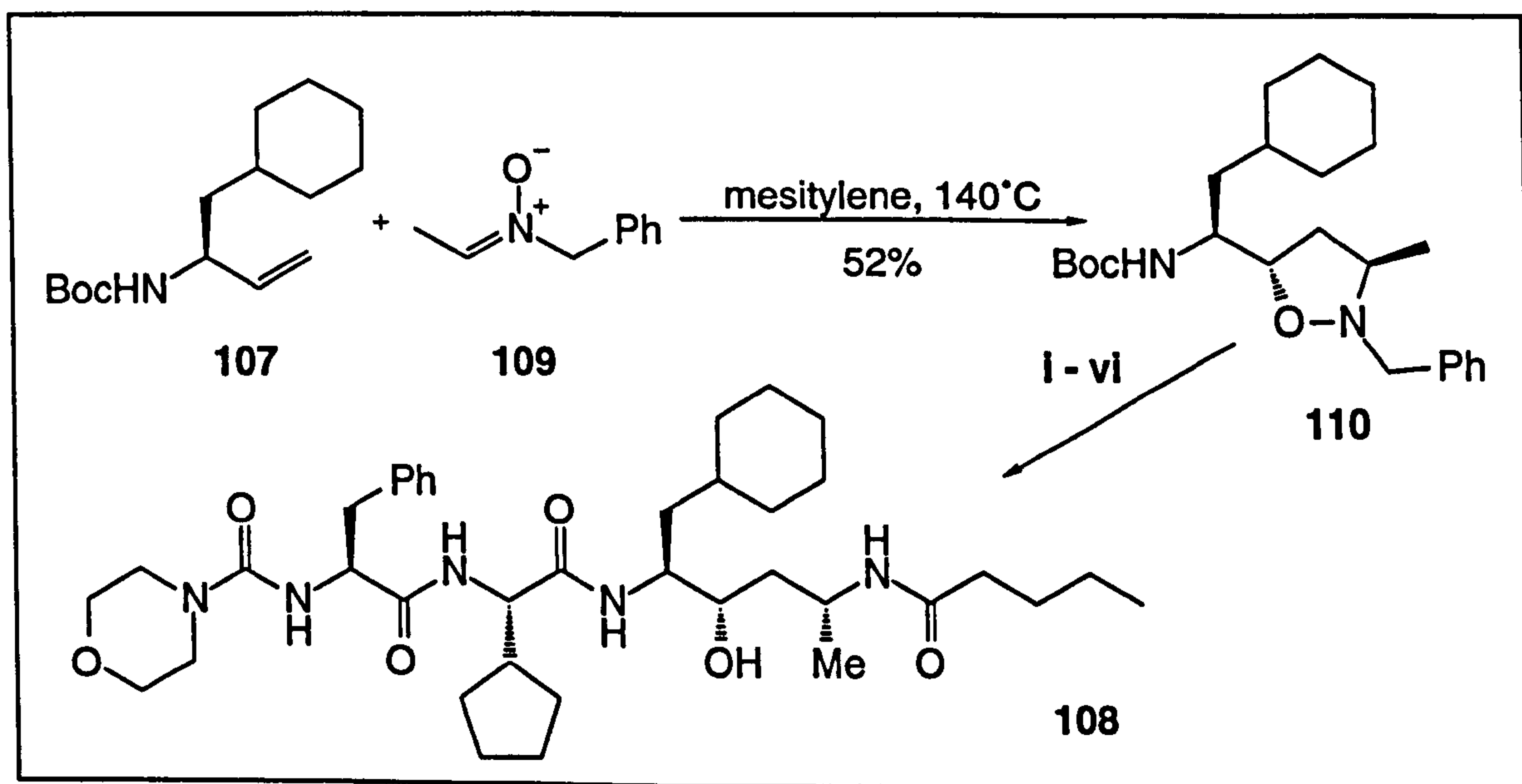
Reagents : i, H_2 , 5 atmos, PdCl_2 , MeOH; ii, $\text{BnOCOC}_2\text{H}_5$, Na_2CO_3 , CH_2Cl_2 ; iii, HIO_4 , THF, H_2O ; iv, Ph_3PMeBr , BuLi, THF; v, H_2 , Pd-C, MeOH.

Scheme 35

Those chiral allylic amines used in 1,3-dipolar cycloaddition reactions have invariably been derived from L- α -amino-acids.¹²⁹⁻¹³⁴ The N-protected allylic amine **107**,

prepared from phenylalanine, was used in the synthesis of the polyamide **108** - a novel renin inhibitor and potential anti-hypertensive agent (Scheme 36).¹³³ The cycloaddition of **107** with N-benzyl-C-methylnitrone **109** gave isoxazolidine **110** after chromatography, before hydrogenolysis of the N-O bond, debenzylation and conversion of the free amine to the pentanamide. The synthesis of **108** was completed by removal of the Boc group and DCC-mediated coupling of this moiety with (S)-cyclopentylglycine and then morpholinocarbonylphenylalanine.

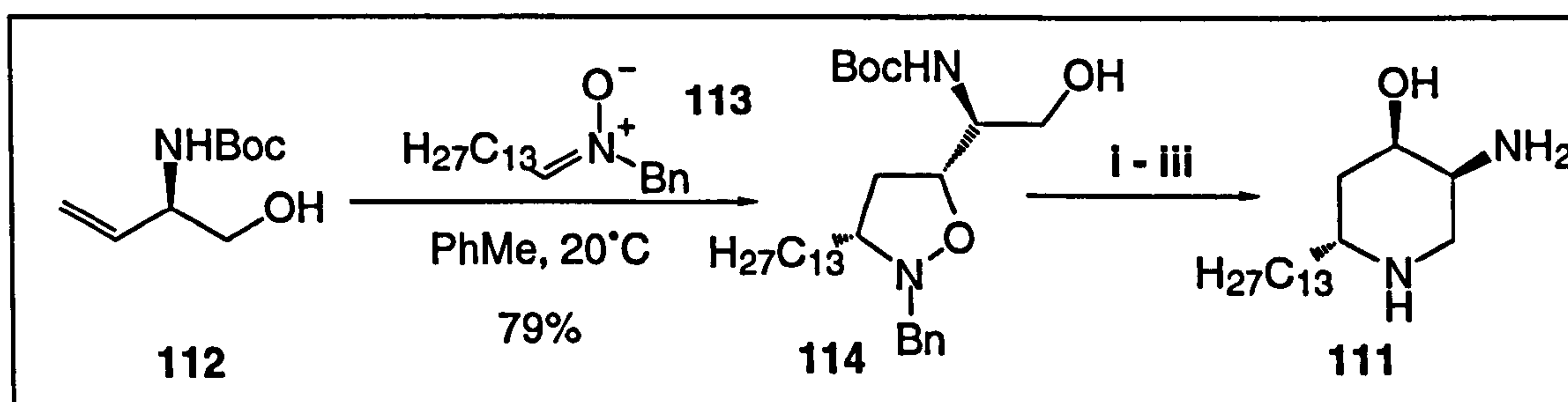
Other research groups have demonstrated the utility of chiral vinyl glycine derivatives; for example, in the preparation of (3*R*)- and (3*S*)-hydroxyornithines and arginines.¹³⁰⁻¹³² Reported yields are high but with little diastereoselectivity (3:2), although the cycloadducts are separable by chromatography. Whitney *et al.* have used a similar strategy in the synthesis of the naturally occurring antitumour antibiotic acivicin.^{149,150}



Reagent : i, HCO₂NH₄, 10% Pd-C, MeOH, 64°C; ii, (n-BuCO)₂O, Et₃N, MeOH; iii, 4M aq. HCl, dioxane; iv, (S)-cyclopentylglycine, DCC, HOBT, ⁱPr₂NEt; v, 4M aq. HCl, dioxane; vi, morpholinocarbonylphenyl-alanine, DCC, HOBT, ⁱPr₂NEt.

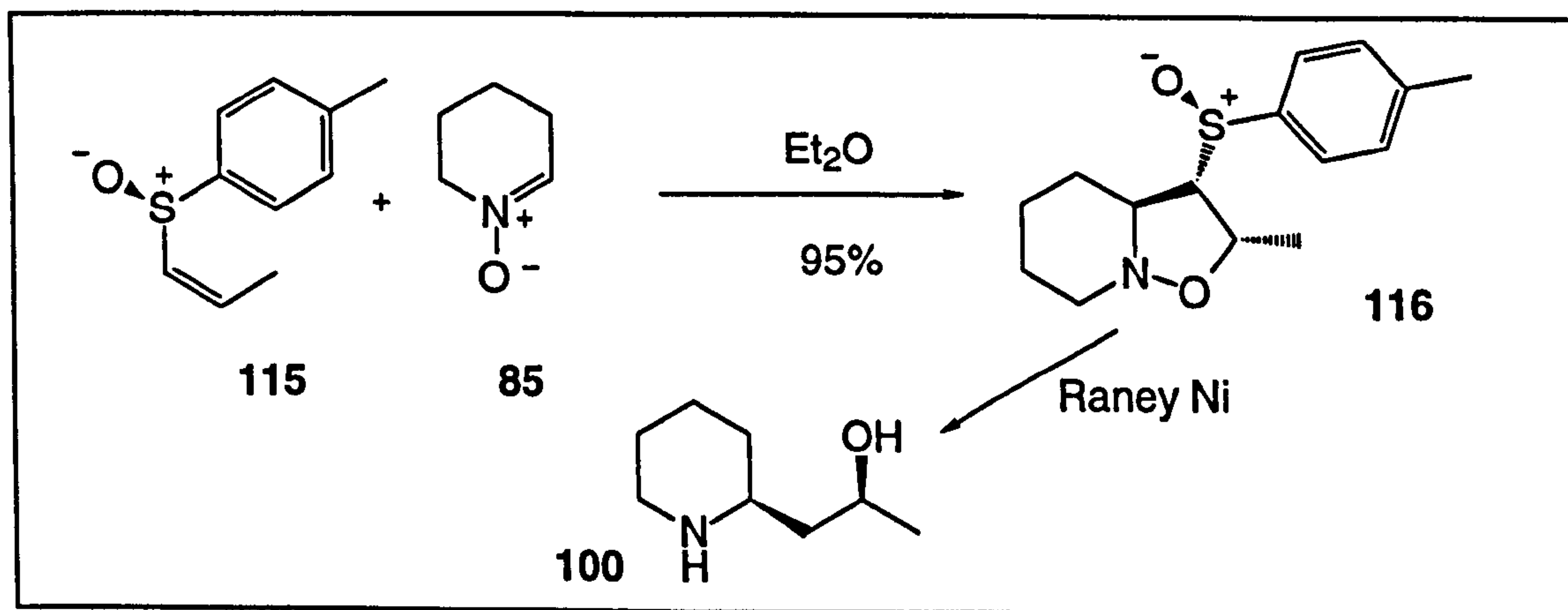
Scheme 36

Japanese workers have developed a large-scale synthesis of the alkaloid (2*R*, 4*R*, 5*S*)-tetrahydropseudodistimin **111** from a chiral vinylglycinol derivative **112** (Scheme 37).¹²⁹ A tetradecanal-derived nitron **113** reacts with allylamine **112** to give a mixture of four isoxazolidines from which the desired isomer **114** is readily separable. Conversion to the desired alkaloid **111** is accomplished in three steps, which compares very favourably with the previously reported 24-step synthesis.¹⁵¹



Reagents : i, MsCl, C₅H₅N, 0°C; ii, 10% Pd(OH)₂-C, MeOH, 20°C; iii, TFA, CH₂Cl₂, 20°C.

Scheme 37

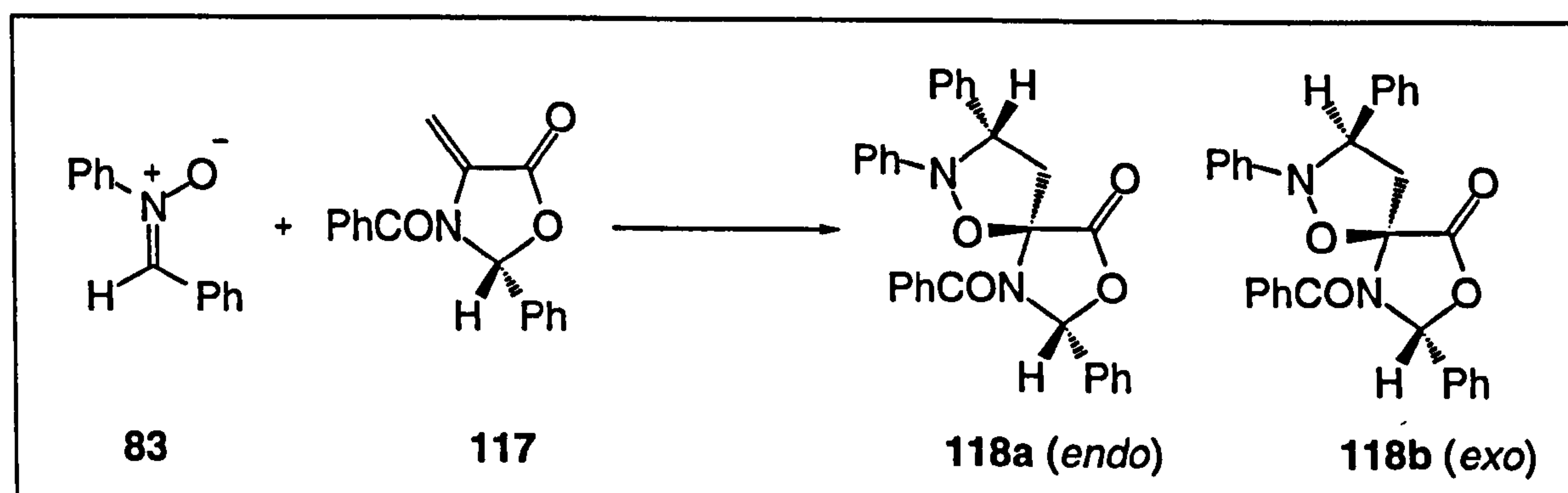


Scheme 38

Reactions involving chiral vinyl sulphoxide dipolarophiles are a less well studied area of nitron cycloaddition chemistry. Rare examples include the synthesis of isophedrines¹³⁶ which has been achieved by Japanese researchers using (*R*)-(+)-*p*-tolylvinyl

sulphoxide whilst Bravo *et al.* have synthesised fluorinated isoxazolidines.¹³⁷ Reaction of 2,3,4,5-tetrahydropyridine-N-oxide **85** with sulphoxide **115** gave a 95% yield of **116** and another isomer (91:9) after a 7-day reaction. Isoxazolidine **116** was converted to (+)-sedridine **100** in a single N-O cleavage and desulphurisation step with Raney Nickel (Scheme 38).¹³⁸

Amongst the more unusual dipolarophiles are the chiral exo-cyclic alkenes of Diazortiz *et al.* and Pyne *et al.* (Scheme 39).^{152,153} For example, reaction of **117** with C,N-diphenylnitrone **83** affords isoxazolidine **118** as a mixture of *endo:exo* isomers in a ratio of 70:30. Both products arise from attack of the nitrone at the face of the alkene which is *anti* to the phenyl substituent.¹⁵³

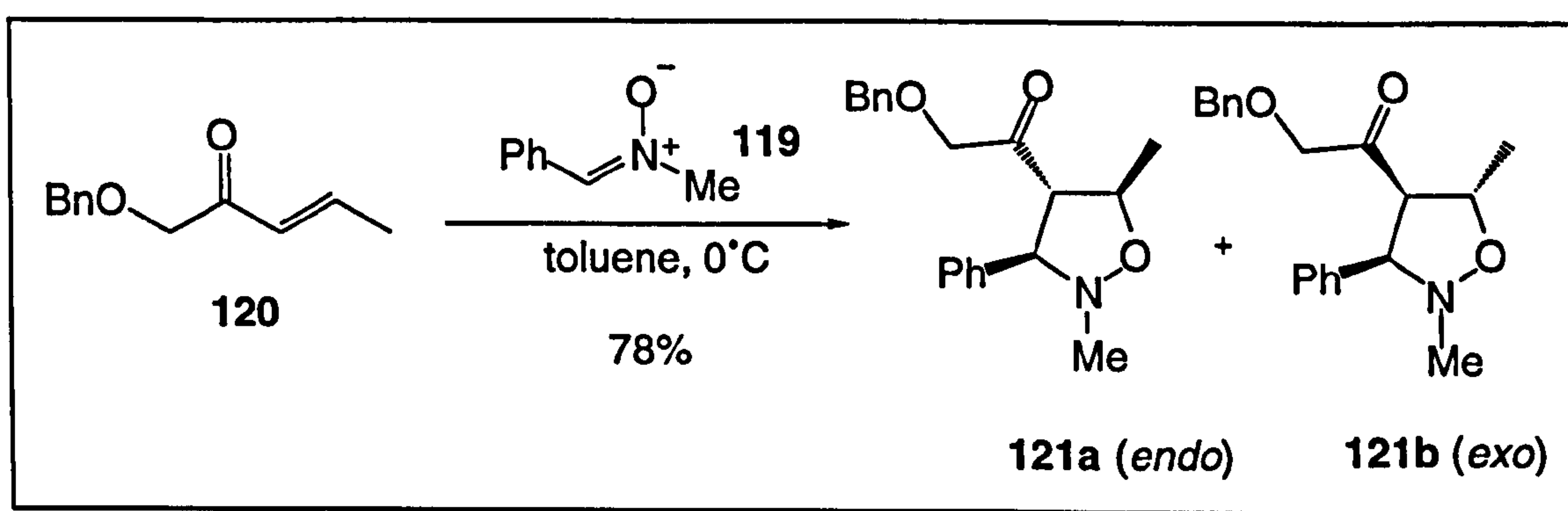


Scheme 39

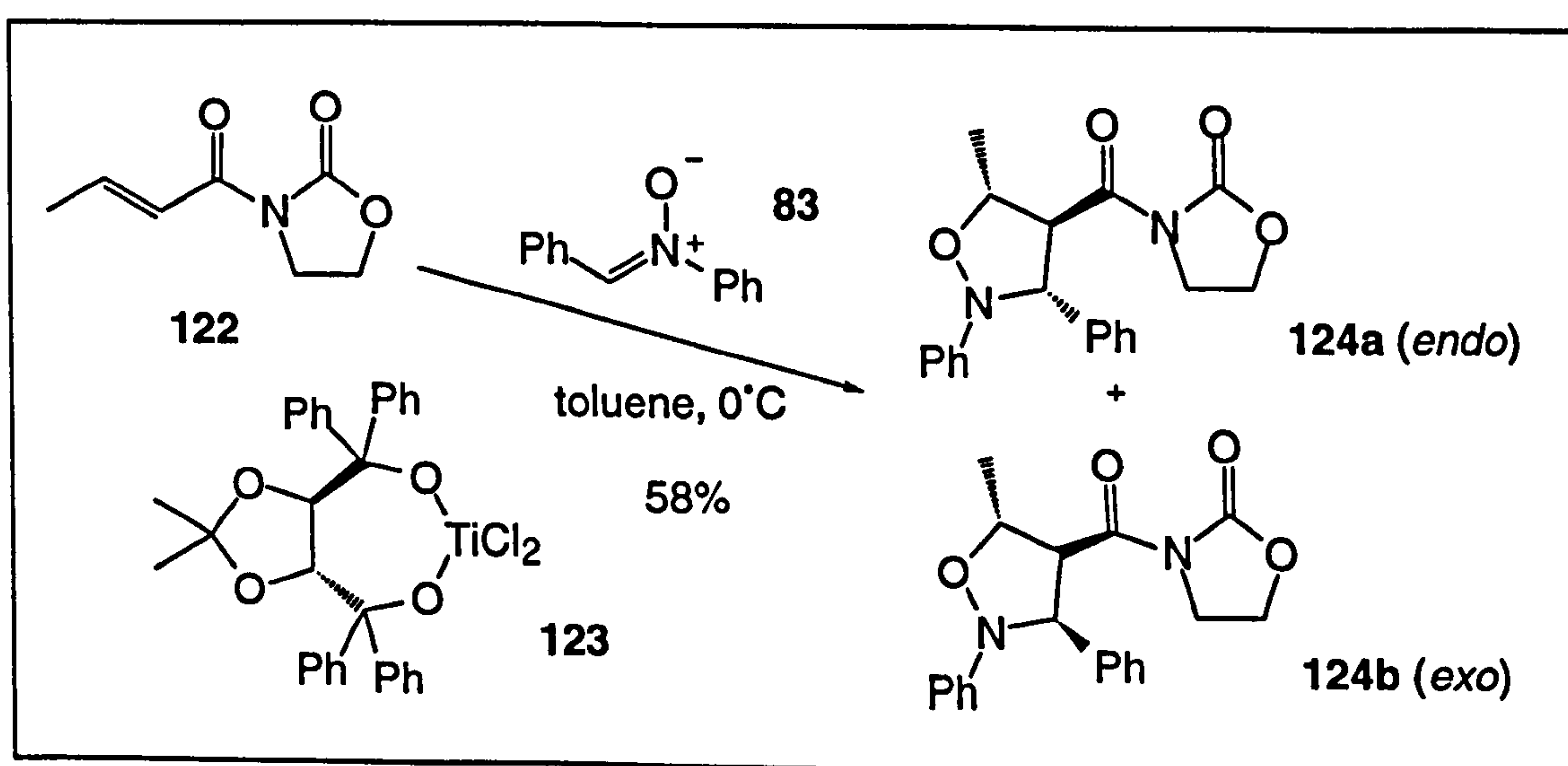
1.3.3 Chiral catalysts

The use of sub-stoichiometric amounts of optically active materials to induce chirality has found broad application in carbo- and hetero-Diels-Alder reactions.¹⁵⁴ However, chiral catalysis of nitrone 1,3-dipolar cycloaddition reactions was until recently a relatively

unexplored area. Important pioneering work^{155,156} was carried out by Kanemasa *et al.* who in 1992 published their investigations of the effect of zinc- and titanium-based catalysts on the reaction of N-methyl-C-phenylnitron **119** with the enone **120** (Scheme 40).¹⁵⁵ The uncatalysed reaction proceeded in 8 hours at 80°C to afford a 40:60 mixture of the *endo* and *exo* 4-keto-isoxazolidines **121a** and **121b** in 78% yield. In their best result, the use of a stoichiometric amount of $\text{Ti}(\text{OiPr})_2\text{Cl}_2$ afforded only a 50% yield of the two isoxazolidines after 32 hours at 0°C, but with an impressive *endo:exo* ratio of 99:1.



Scheme 40



Scheme 41

In a more recent example, Jørgensen showed that C,N-diphenylnitrone **83** reacts with N-crotonyl-2-oxazolidinone **122** in the presence of Ti-TADDOL catalyst **123** to give predominantly the *exo*-cycloadduct **124b** in high yield (94%) and fair diastereomeric excess (58%) (Scheme 41).¹⁵⁷ The same group later applied Mg(II) and Cu(II)-derived *bis*-oxazoline catalysts to similar transformations to achieve an enantiomeric purity of the isoxazolidine cycloadduct of up to 82%.¹⁵⁸

Chapter 2

Results and Discussion

2.1 Strategy

From the foregoing examples from the recent literature (Section 1.3), it can be seen that nitron reagents **8** carrying a chiral auxiliary on nitrogen have the potential for highly effective asymmetric induction in 1,3-dipolar cycloaddition reactions (Figure 16). As we have shown, their usefulness is often limited by the conformational mobility about the C- or N-to-auxiliary bond. The use of chiral cyclic nitrones **9** introduces a means of rotational restraint and enforces the diastereofacial influence of the auxiliary.

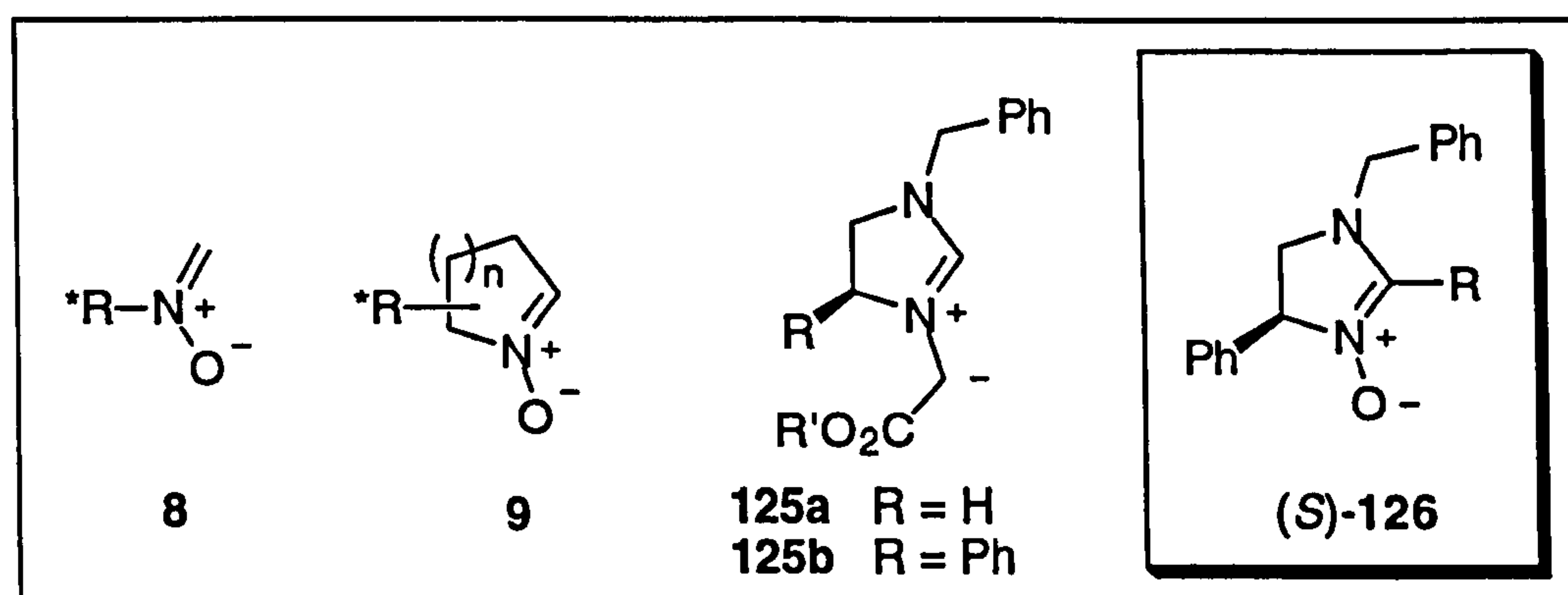
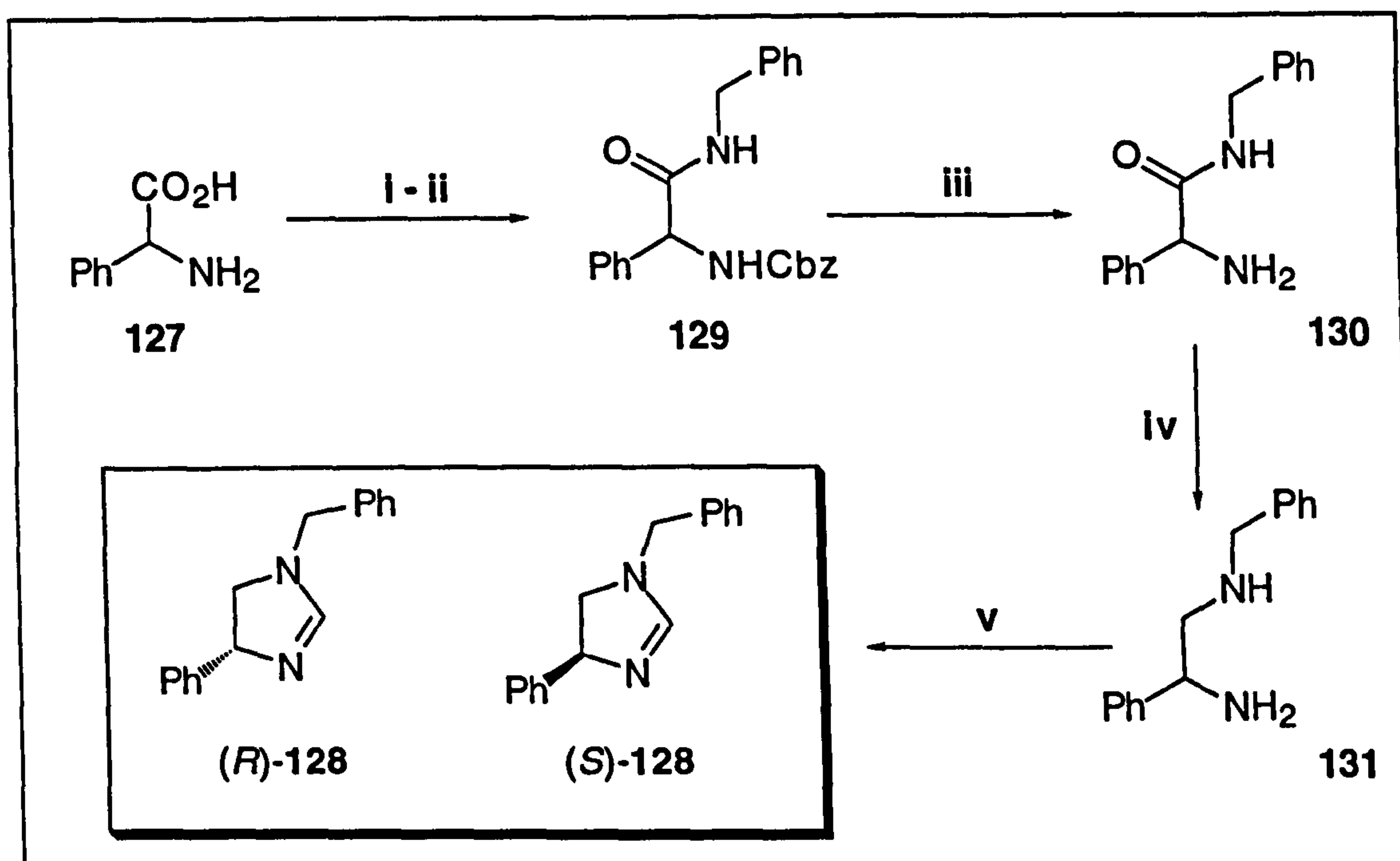


Figure 16 : The diastereofacial nature of 1,3-dipoles based on chiral 2-imidazolines.

Previous workers in the Jones group have prepared azomethine ylide 1,3-dipoles based on the 2-imidazoline (or 4,5-dihydroimidazole) moiety **125a** as a template. These reagents undergo 1,3-dipolar cycloaddition reactions with a number of dipolarophiles, offering access to functionalised pyrrolidines, pyrroles and pyrroloimidazoles.¹⁵⁹⁻¹⁶¹ These workers were able to demonstrate that the optically active ylide **125b** and its enantiomer show complete facial discrimination in their 1,3-dipolar cycloaddition reactions.^{162,163} A simple two-step template removal strategy was subsequently developed to complete this elegant synthetic route to optically active substituted pyrrolidines.¹⁶⁴ In

order to capitalise on the properties of this 2-imidazoline moiety as a chiral template, we proposed to prepare the novel chiral nitron 1,3-dipoles **126** and their enantiomers in order to investigate their 1,3-dipolar cycloaddition chemistry.

2.1.1 Homochiral 2-imidazoline azomethine ylides

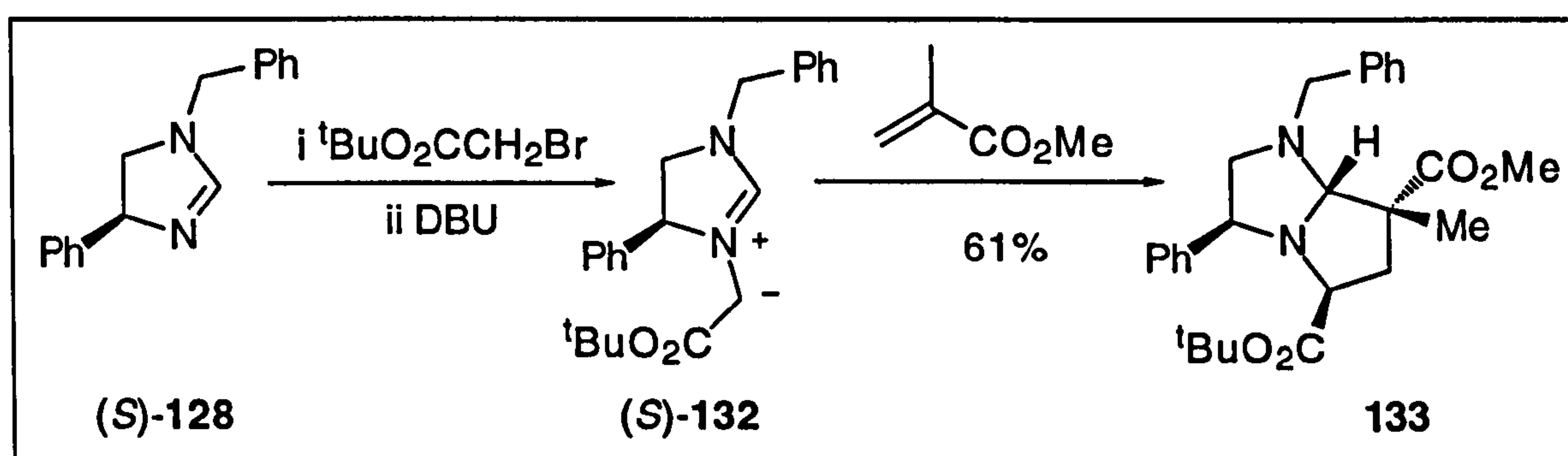


Reagents : i, $\text{PhCH}_2\text{OCOC}_2\text{H}_5$, aq. NaOH; ii, N-methylmorpholine, $\text{EtOCOC}_2\text{H}_5$, BnNH_2 ; iii, H_2 , Pd-C; iv, $\text{BH}_3\cdot\text{THF}$; v, $\text{HC}(\text{OEt})_3$, *p*-TsOH.

Scheme 42

The synthesis of these 1,3-dipoles uses (*R*)- and (*S*)-phenylglycine **127** as the chiral source and proceeds *via* the 2-imidazolines **128** (Scheme 42) from which the azomethine ylides are generated for use *in situ*.¹⁶³ The cheap, commercially available enantiopure amino-acids were first protected on nitrogen as the benzyloxycarbonyl (Cbz) derivatives in

high yield using benzyl chloroformate. These carbamates could then be used without purification to prepare the N-benzyl amides **129** via the mixed anhydrides formed with ethyl chloroformate. Quantitative hydrogenolysis of the Cbz-protection over palladium on carbon to give the amino amides **130** was followed by reduction of the carbonyl groups with borane-tetrahydrofuran complex ($\text{BH}_3\cdot\text{THF}$) to afford the diamines **131**. The synthesis was completed by heating the diamines **131** with triethyl orthoformate in the presence of catalytic *p*-toluenesulfonic acid to generate the homochiral 2-imidazolines (*R*)- or (*S*)-**128** in 46% or 52% overall yield from (*R*)- or (*S*)-**127**, respectively.



Scheme 43

The azomethine ylides (*R*)- and (*S*)-**125b** were generated by a one-pot process which begins by alkylation of the 2-imidazolines (*R*)- and (*S*)-**128** in refluxing THF with an activated haloalkane such as methyl or *tert*-butyl bromoacetate under anhydrous conditions (Scheme 43). In the presence of 3 equivalents of the dipolarophile, 1 equivalent of DBU is added over 4 hours to allow immediate cycloaddition of the ylide as soon as it is formed. For example, the azomethine ylide (*S*)-**132** was prepared from (*S*)-**128** and *tert*-butyl bromoacetate, and 1,3-dipolar cycloaddition with methyl methacrylate afforded the hexahydropyrroloimidazole **133** (61%).

The major product in the 1,3-dipolar cycloaddition reactions to the chiral azomethine ylide dipoles (*R*)- or (*S*)-**125b** was found to be the isomer arising from attack at the less hindered face of the ylide and *via* the *endo* transition state (Figure 17). This was determined using nuclear Overhauser enhancement (nOe) spectroscopy. This NMR technique, which will be discussed in more detail in Section 2.3, allows us to determine which protons in the ^1H spectrum are adjacent *through space*.

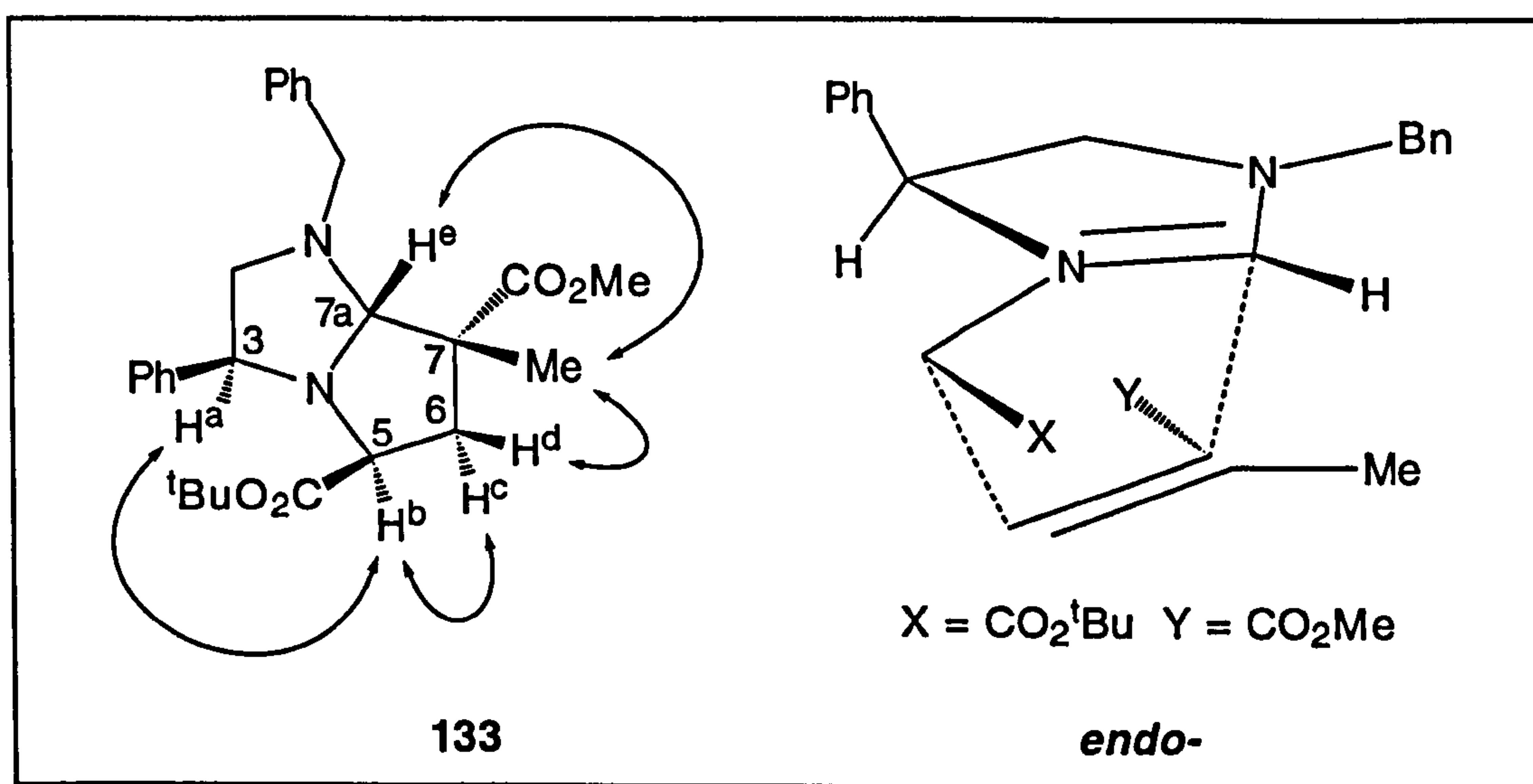
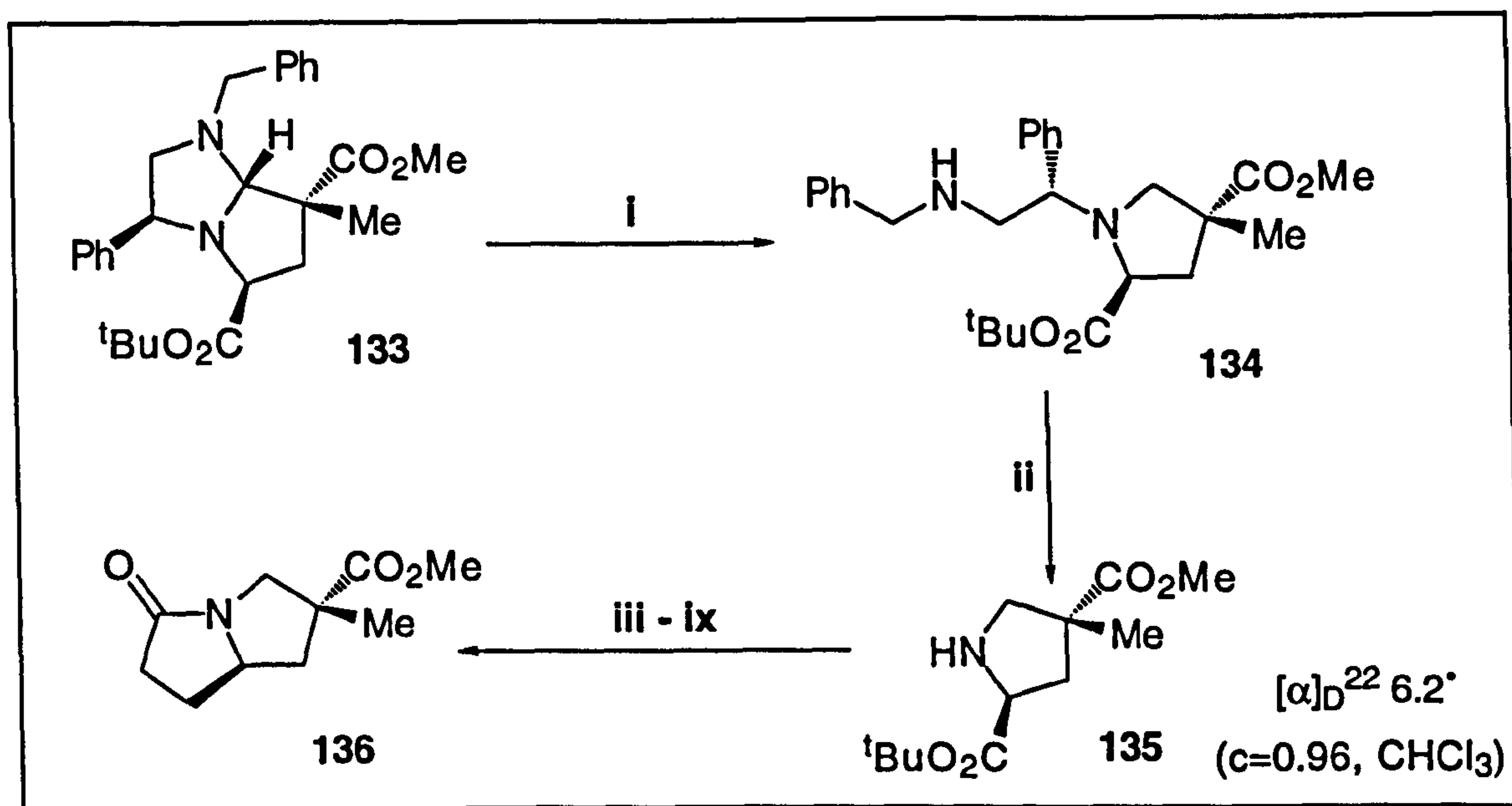


Figure 17 : Assignment of stereochemistry of **133** by nOe and the *endo* transition state from which it arises.

In this way, it was found that for adduct **133**, through-space interaction existed between the protons connected by arrows in Figure 17; that is, between H^a , H^b and H^c , and between H^d , the C-7 methyl group and H^e . Thus, with the C-3 stereochemistry known, we can see that H^a , H^b and H^c lie on the lower face of **133**, with H^d , the C-7 methyl group and H^e on the top face. The configuration of the bridgehead proton at C-7a (H^f) shows that the dipolarophile is directed to the lower face of the ylide (*S*)-**132**; reaction at the upper face is made unfavourable by the bulk of the phenyl group at C-3. The stereochemistry at C-7

would arise from the *endo* transition state, suggesting a secondary orbital interaction between the 1,3-dipole and the ester functionality stabilising this transition state geometry prior to bond formation. From the stereochemistry at C-5, we can see that the X-substituent is *anti* to the C-3 to N-4 bond as drawn for the *endo* transition state in Figure 17.



Reagents : i, NaCNBH₃, pH3; ii, H₂, Pd-C; iii, PhCH₂OCOCl, Et₃N, DCM; iv, TFA; v DCCl, HOSu, THF then NaBH₄, THF; vi, TPAP, NMO, DCM; vii, (EtO)₂POCH₂CO₂Et, NaH, THF; viii, H₂, 60psi, 10% Pd-C, MeOH; ix, Xylene, Δ.

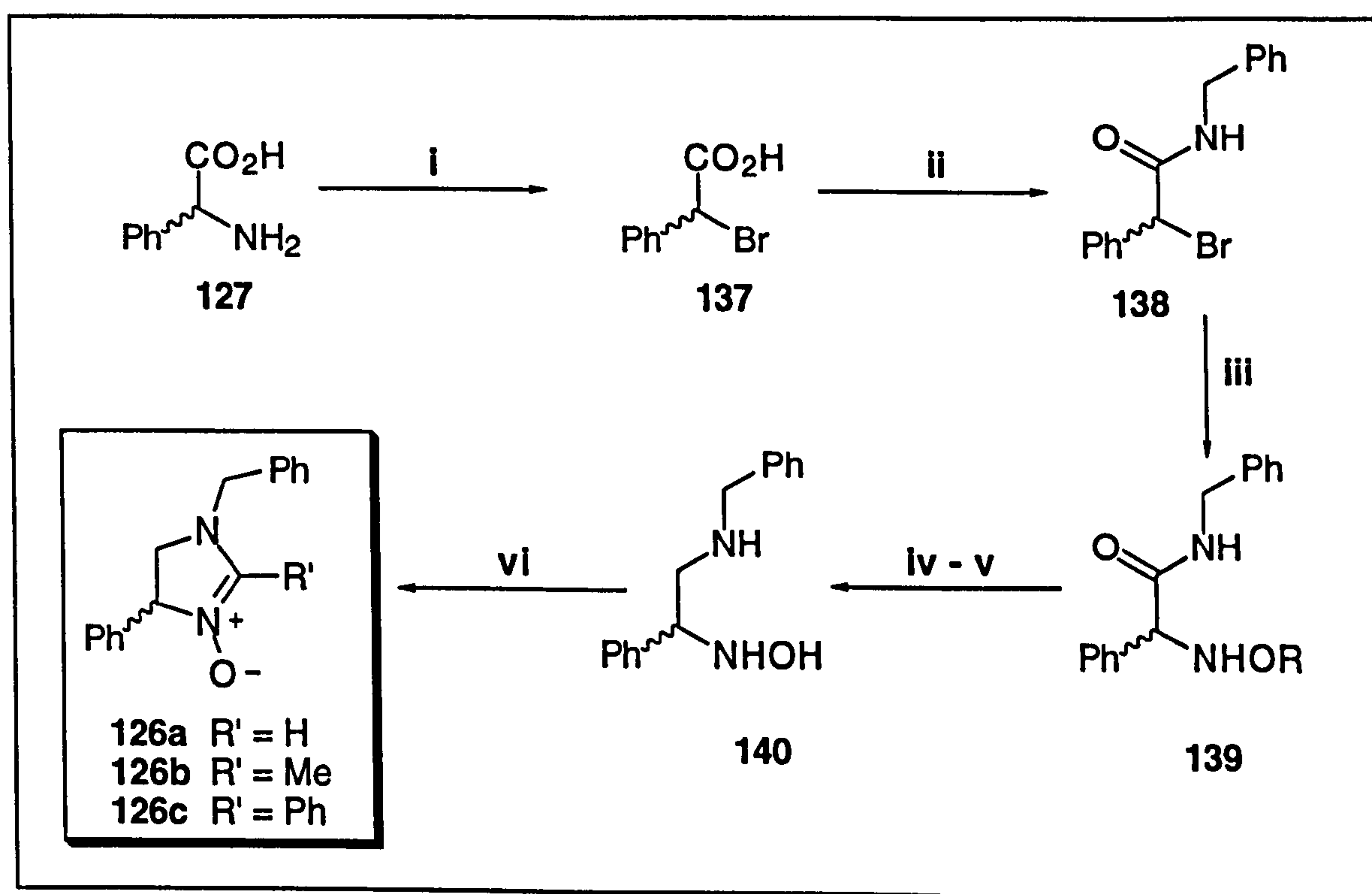
Scheme 44

Removal of the imidazoline chiral template was achieved in two steps (Scheme 44).¹⁶⁴ Firstly, reduction of the amination moiety of 133 with sodium cyanoborohydride at pH3 afforded a near quantitative yield of the pyrrolidine 134. This was followed by hydrogenolysis of the pyrrolidine N-benzyl moiety over Pearlman's catalyst (palladium hydroxide on carbon) to afford the proline derivative 135. The differentiated ester protection at C-2 and C-4 should allow manipulation to take place at either position. As an illustration,

pyrrolizidinone **136** was prepared by conversion of the C-2 ester to the aldehyde and chain extension by the Wadsworth-Emmons reaction, followed by thermal cyclisation to the lactam.

In conclusion, it is clear that this 2-imidazoline chiral template offers complete diastereofacial selectivity in azomethine ylide cycloaddition reactions, making this a powerful strategy for rapid access to enantiopure natural products.

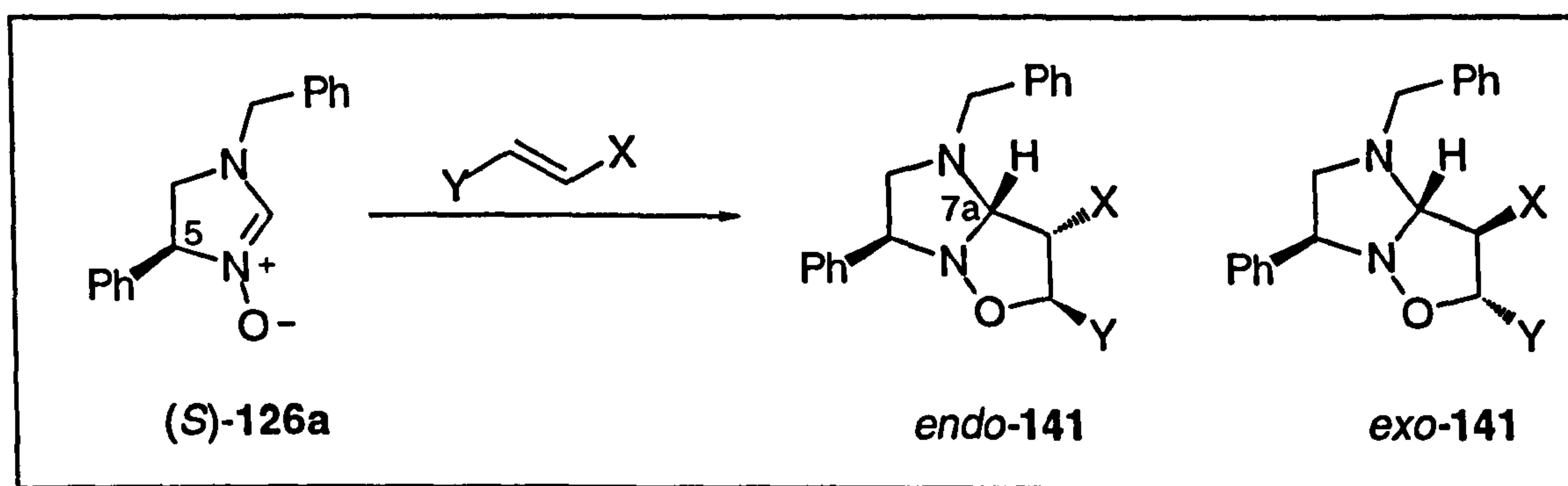
2.1.2 Homochiral 2-imidazoline nitrones



Reagents proposed : i, NaNO_2 , HBr; ii, EtOCOCl , N-Methylmorpholine, BnNH_2 ; iii, $\text{NH}_2\text{OR} \cdot \text{HCl}$, base; iv, $\text{BH}_3 \cdot \text{THF}$; v, R = Bn, H_2 , Pd-C; vi, $\text{R}'\text{C}(\text{OEt})_3$, H^+ .

Scheme 45

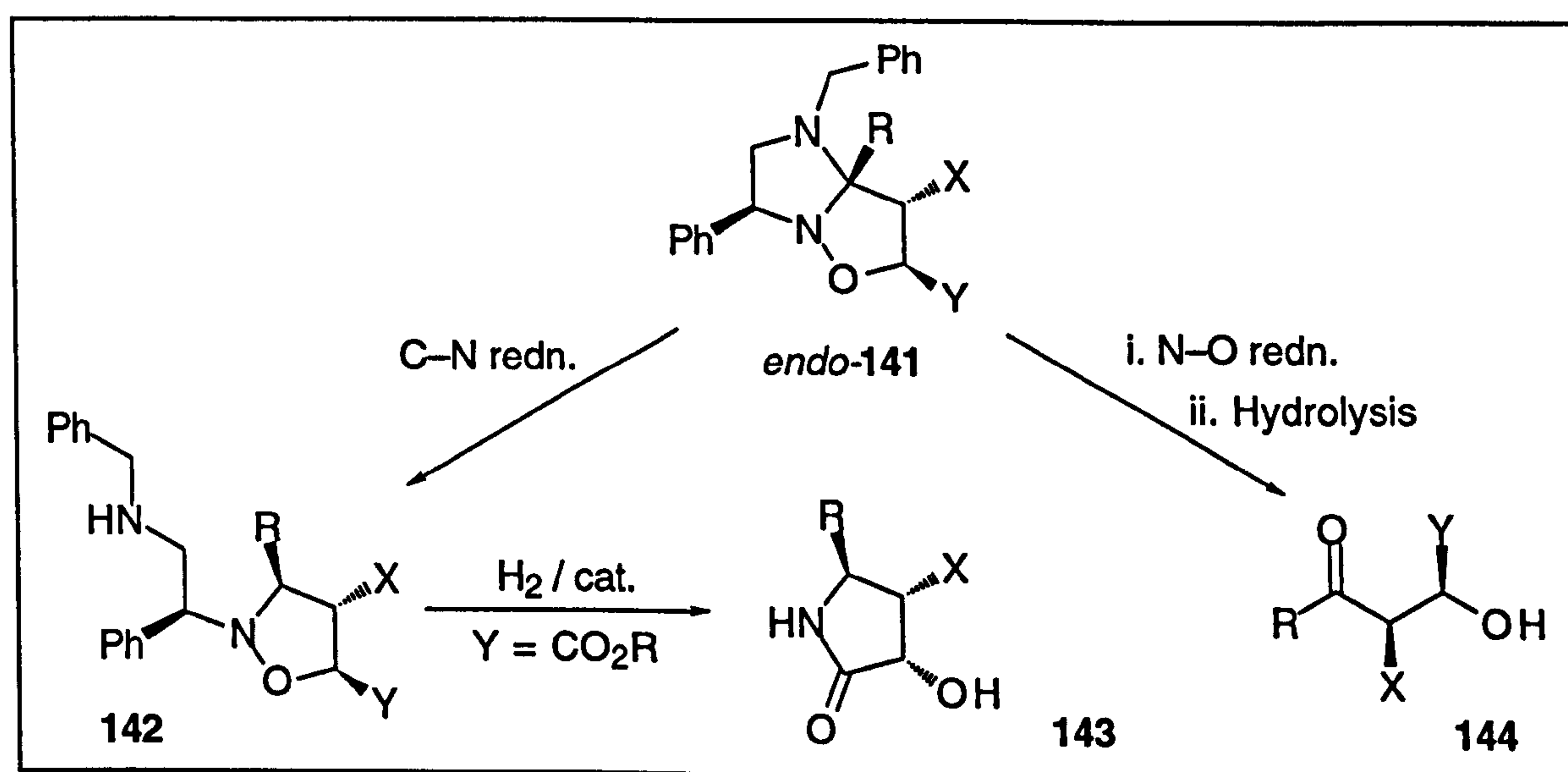
With this azomethine ylide methodology in hand, we initially proposed to prepare the related homochiral nitronone dipoles (*R*)- and (*S*)-**126** using a revised and novel route (Scheme 45), again using phenylglycine as the chiral source. The plan was to first brominate *via* diazotisation in the presence of aqueous HBr to afford the α -bromoacid **137**. This centre is now set up for nucleophilic substitution by an O-alkylhydroxylamine (for example, R=Bn). The bromo amide **138** would be provided by reaction of the acid chloride from **137** with benzylamine before amide reduction with $\text{BH}_3\cdot\text{THF}$ followed by catalytic hydrogenolysis of the N-benzyl protecting group to afford the amino hydroxylamine **140**. Ring closure of this key intermediate would be effected with triethyl orthoesters to access nitrones **126** with defined C-2 substitution. We proposed to prove our methodology on racemic material before applying it to the synthesis of the enantiopure nitrones.



Scheme 46

Once we had developed a robust synthesis of our novel 2-imidazoline nitronone reagents, we would examine the scope of their 1,3-dipolar cycloaddition reactions with a wide range of dipolarophiles. Our first priority would then be to determine whether the cycloaddition proceeds with facial selectivity and regioselectivity. We hoped to be able to chart the electronic requirements of the dipolarophile by reaction with doubly- and triply-bonded species carrying electron-withdrawing, conjugating or electron-donating substituents

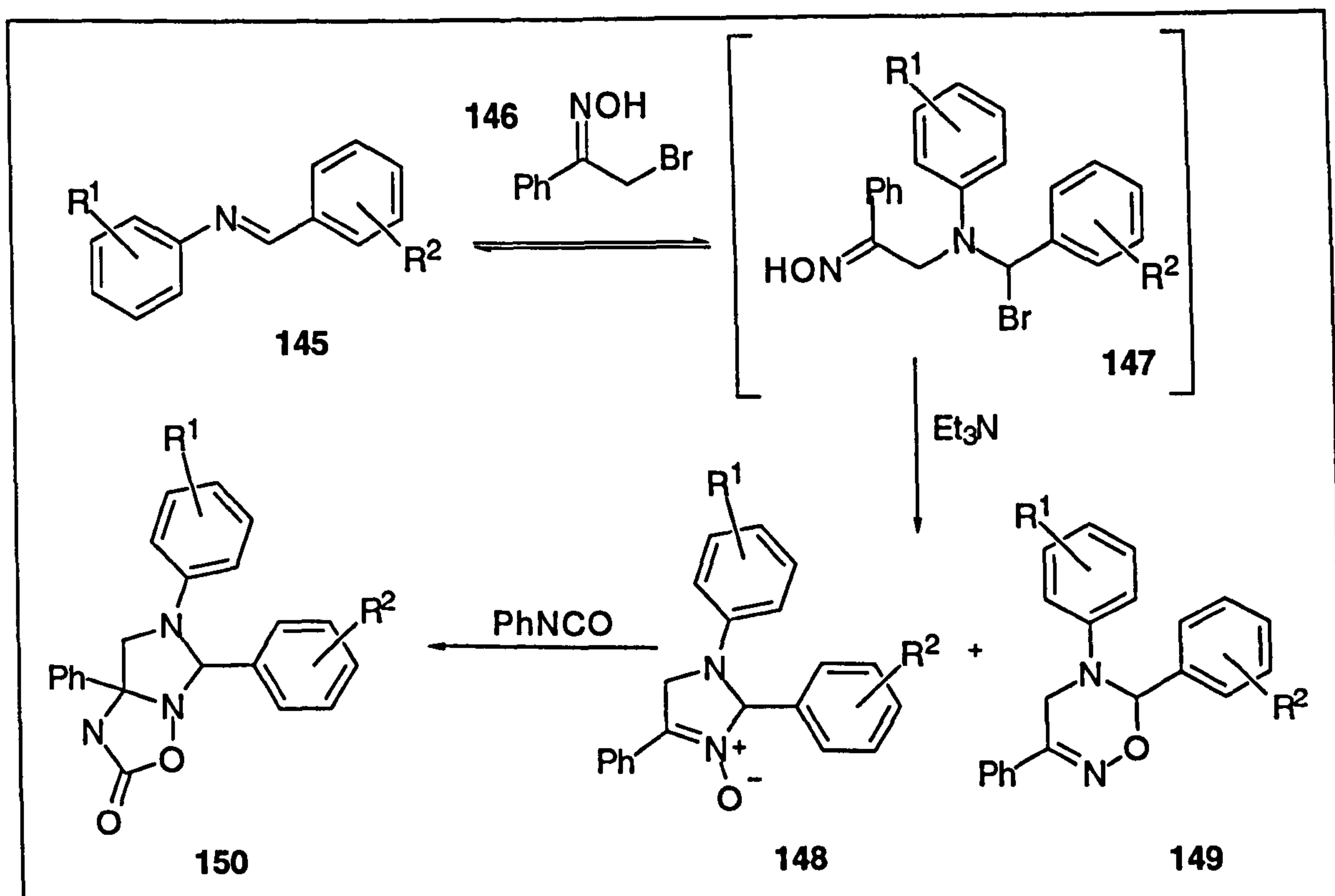
and we will discuss our findings in terms of Frontier Molecular Orbital theory. We proposed that a 1,2-disubstituted alkene would add to the less hindered face of these nitrones. Therefore, we suggest that the reaction of (*S*)-**126a** (R=H) with such an alkene would afford the isoxazolidine **141** in which the stereochemistry at C-7a is defined by the C-5 stereochemistry of the dipole **126a** (Scheme 46). We planned to investigate the cycloaddition reactions of C-2 functionalised 2-imidazoline nitrones, for example **126b** (R=Me) and **126c** (R=Ph). We will ascertain the preferred transition state geometry from the stereochemistry of the isolated isoxazolidine products. Analogy to the corresponding azomethine ylides would predict *endo* approach to be dominant here, that is to say the isoxazolidine *endo*-**141** would be the major product of the reaction of a *trans*-disubstituted alkene with nitrone (*S*)-**126a**.



Scheme 47

We planned to remove the chiral template by a two-step protocol of amination reduction to **142** then hydrogenolysis (Scheme 47). We will take advantage of the synthetic track record of isoxazolidines based on N-O bond cleavage and will seek to fulfil the potential of

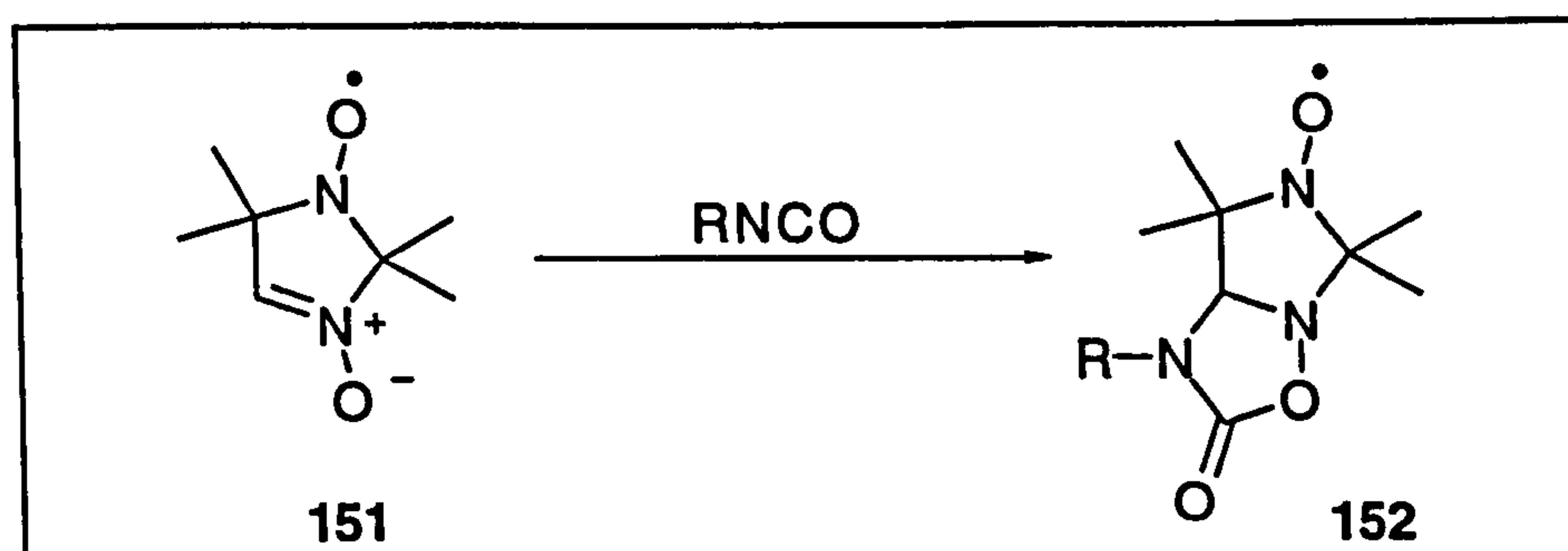
our cycloadducts for recyclisation, for example *via* lactamisation to afford homochiral substituted pyrrolidinones **143**. Alternatively, one can envisage cleavage of the N–O bond with acid hydrolysis of the cycloadducts to unmask carbonyl functionality and access enantiopure substituted β -hydroxyaldehydes and ketones **144**.



Scheme 48

To the best of our knowledge, 1,3-dipolar cycloaddition reactions of 2-imidazoline nitrones are unknown in the literature although, as we shall see, closely related reagents have been prepared. In contrast, the 1,3-dipolar cycloaddition reactions of 3-imidazoline nitrones have been investigated by three separate research groups.¹⁶⁵⁻¹⁷³ Most recently, Coskun *et al.* have prepared a series of 3-imidazoline nitrones from the corresponding imines (Scheme 48).^{174,175} The imine **145** is alkylated with *syn*-2-bromoacetophenone oxime **146** to generate the brominated species **147** which cyclises on addition of triethylamine to

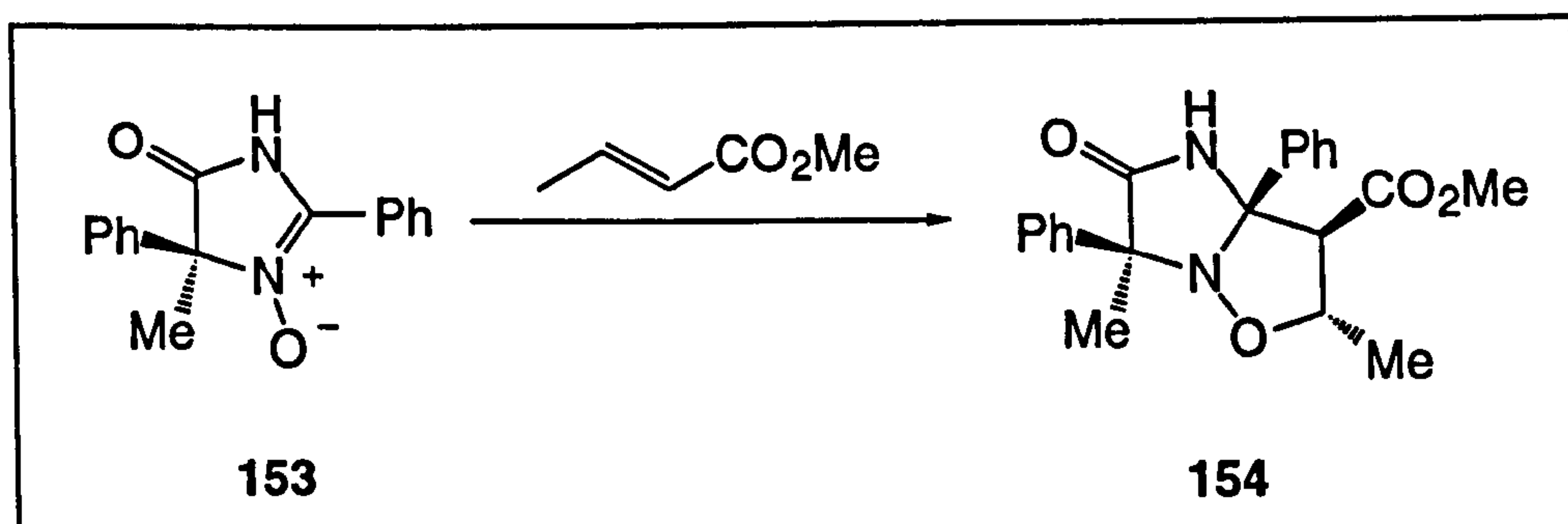
afford the 3-imidazoline nitrones **148** in poor yields (22-31%). The 5,6-dihydro-4*H*-1,2,5-oxadiazines **149** were also isolated in small, as yet unreported, yields. A selection of these 3-imidazoline nitrones has been utilised in 1,3-dipolar cycloaddition reactions with styrene or with aryl isocyanate dipolarophiles to afford the adducts **150**. These reactions afford fair (49-50%) and excellent yields (90-100%) of each type of cycloadduct after 72 hours in refluxing toluene or 2.5 hours in refluxing acetonitrile respectively.¹⁶⁵⁻¹⁶⁷



Scheme 49

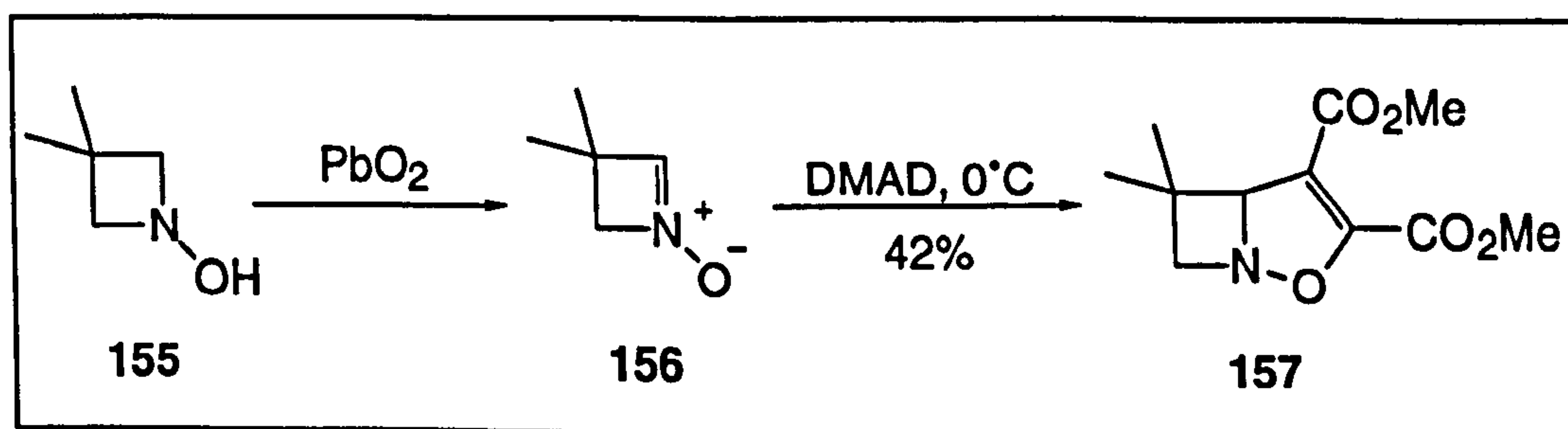
Hungarian, French and Russian researchers have reported the preparation of 2- and 3-imidazoline nitrones as intermediates in the synthesis of imidazoline-derived nitroxyl radicals.^{168,176-185} These highly stable radicals have been used as spin labels and probes for the study of other radical species (for example, NO•), and as paramagnetic ligands in the chemistry of coordination compounds. The 3-imidazoline nitrones of Volodarsky *et al.* have been shown to undergo a 1,3-dipolar cycloaddition reaction with isocyanates^{168,169} and alkenes,^{168,170,171}. For example, the 2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl radical **151** reacted with isocyanates to afford the oxadiazolinone cycloadducts **152** (Scheme 49).¹⁶⁹ Sharma *et al.* have prepared substituted 3-imidazoline nitrones from diazabutadienes and nitrostyrenes.¹⁷² These workers have also used these reagents to synthesise

functionalised N-oxides of imidazole which react with DMAD to afford dihydroimidazoisoxazole cycloadducts.¹⁷³



Scheme 50

Chmielewski *et al.* prepared a range of 2-imidazolinone nitrones based on the work of Toda *et al.*¹⁸⁶ who had reported their synthesis of these reagents as intermediates in the preparation of nitroxide radicals. The Polish group described the reaction of their nitrones with a number of dipolarophiles including acrylate esters, styrene and phenyl isocyanate, from which they isolated the desired cycloadduct in each case.¹⁸⁷ For example, the 2,5,-diphenyl-5-methyl-2-oxo-imidazolin-1-oxide **153** was reacted with excess methyl crotonate in refluxing toluene for 10 hours to produce imidazoisoxazol-2-one **154** in 95% yield (Scheme 50). The assignment of their stereochemistry was based on earlier observations where similar nitrones added *via* the *exo* transition state.



Scheme 51

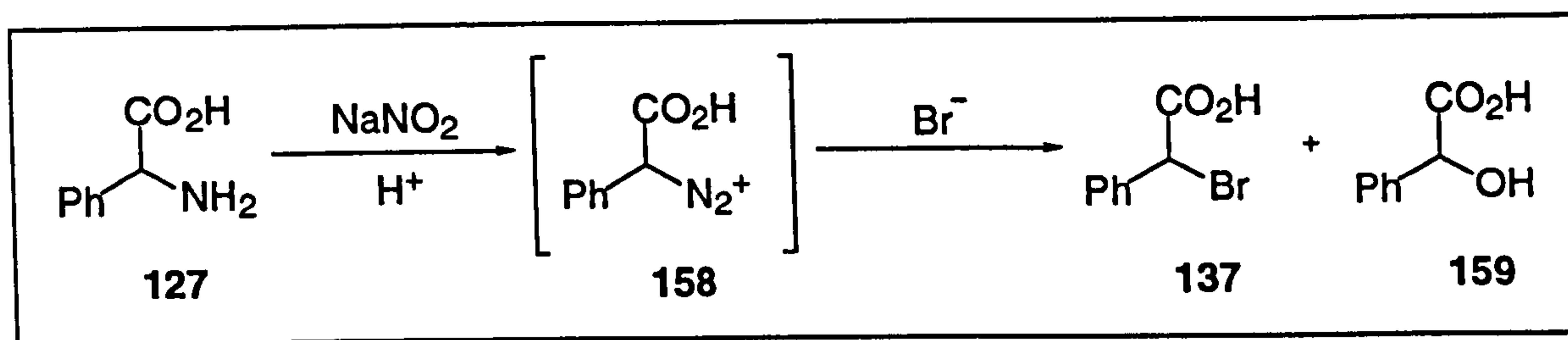
The chemistry of nitrones based on piperidine and pyrrolidine rings is well-documented in the literature. A number of research groups have now reported the synthesis of the unusual 4-membered heterocyclic nitrones.¹⁸⁸⁻¹⁹² Black *et al.* have prepared these azetidine nitrones by the intramolecular cyclisation of γ -tosyloxy oximes.¹⁸⁹ Elsewhere, Reinhoudt has demonstrated that oxidation of N-hydroxyazetidines such as **155** with lead(IV) oxide affords the azetine-1-oxides **156** (Scheme 51).^{188,190,191} They went on to prove their utility in a 1,3-dipolar cycloaddition reaction of **156** with DMAD at 0°C to afford the isoxazoline cycloadduct **157** in a yield of 42%.

Having established the novelty and feasibility of our proposed 2-imidazoline nitrone reagents from this reference to the literature, the following section will detail the results of our investigations.

2.2 Synthesis of 2-imidazoline nitrones

In this section, we will show how our synthetic route to 2-imidazoline nitrones was developed and how these reagents were applied in 1,3-dipolar cycloaddition reactions. A common strategy of nitrone synthesis is direct oxidation of the corresponding imine and our attempts in this area will be presented at the end of this section along with other attempted syntheses.

2.2.1 Approaches from 2-phenylglycine



Scheme 52

As we have shown (Section 2.1), our initial starting point for the synthesis of nitrones containing the 2-imidazoline moiety was 2-phenylglycine **127**. We proposed to introduce the hydroxylamino functionality at the α -position of this amino acid *via* 2-bromo-2-phenylacetic acid **137** (Scheme 52). Our initial strategy was to take advantage of the well-studied α -deaminative halogenation reactions of amino acids^{193,194} to form intermediate **137** with control of configuration and then perform nucleophilic substitution with inversion using a hydroxylamine.¹⁹⁵⁻¹⁹⁸ Bromination of racemic 2-phenylglycine as a model was thus performed by diazotisation with aqueous sodium nitrite at 0°C in the presence of conc.

HBr such that the diazonium species **158** was immediately quenched with bromide. However, the aqueous reaction conditions meant that we were often unable to prevent formation of the α -hydroxy acid (mandelic acid) **159** by attack of water on the diazonium intermediate. Fortunately, this impurity was easily separated from the desired product **137** by column chromatography on silica gel.

Entry	Ph-Gly (grams)	NaNO ₂ (equivs.)	H ₂ O:c.HBr (v/v)	137:159 (moles)	Yield of 137 (%)
1	2.0	1.1	1:3.33	18:1	22
2	0.5	1.1	1 : 2	12 : 1	44
3	2.0	1.1	1 : 2	8 : 1	20
4	1.0	1.1	1 : 1	3.7 : 1	6
5	10.0	1.1	1 : 1	-	0
6	2.0	1.1	1.6 : 1	2.4 : 1	32
7	5.0	1.1	2 : 1	1.7 : 1	24
8	5.0	1.1	5 : 1	2 : 1	67

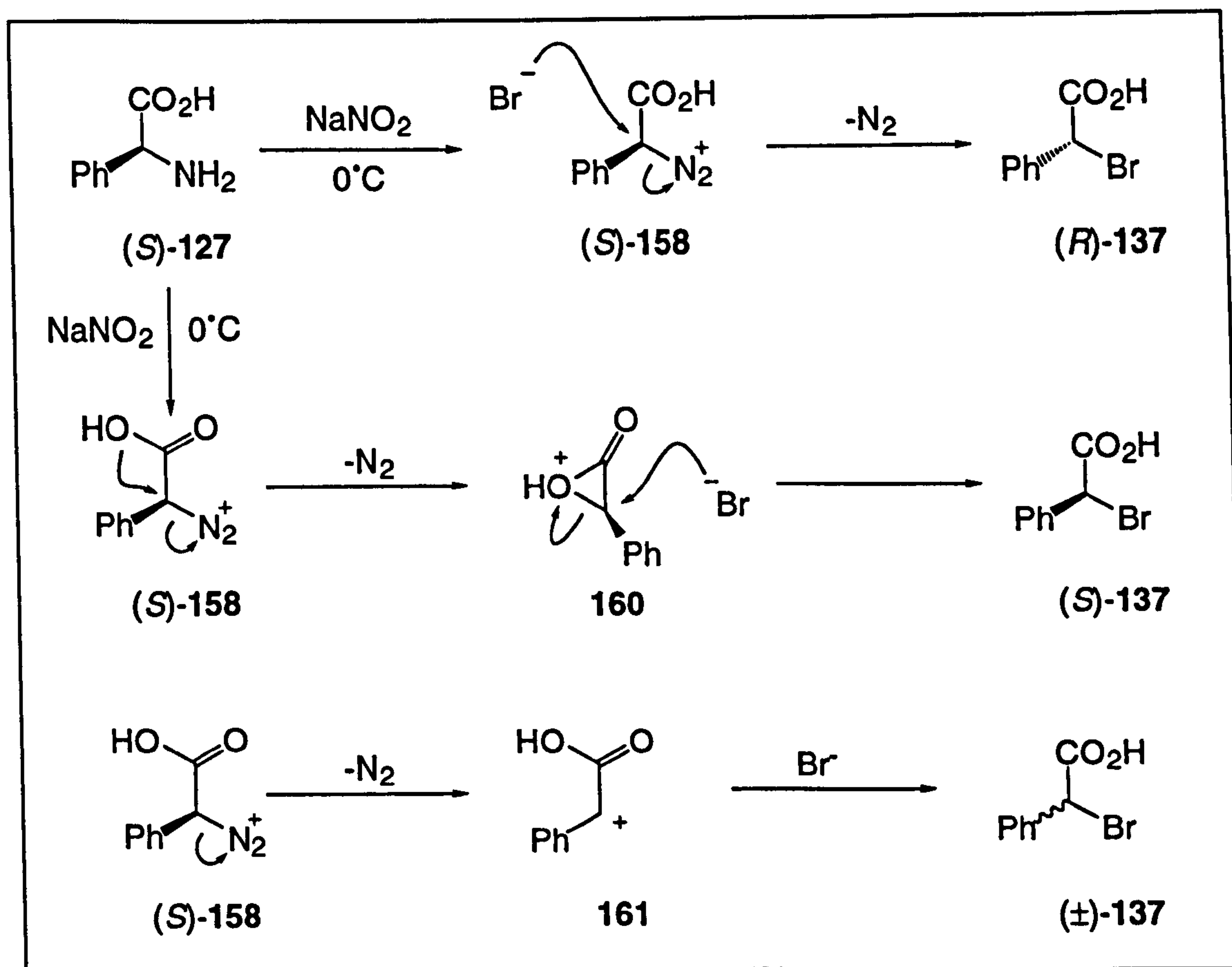
Table 2 : Effect of solvent mixture on yield and purity of 137.

Our efforts towards optimisation of this reaction centred on the relative proportions of water and conc. HBr (Table 2). In a general procedure, 2-phenylglycine **127** was dissolved in 75% of the total water used and treated with all of the conc. HBr. The solution was cooled to 0°C and treated with a solution of sodium nitrite (1.1 equivalents) in the remaining 25% of the water. After 30 minutes at 0°C, the solution was warmed to room

temperature and stirred for a further hour. The resultant mixture was diluted with DCM and water before extraction with further DCM. It was found that a large excess of water in the reaction solvent gave the highest yield of **137** (67%) but also gave the least favourable product mixture (2:1 mixture of **137** & **159** respectively) (entry 8). Experiments performed in excess conc. HBr (entries 1, 2 & 3) gave relatively little mandelic acid **159** but yields of the bromide **137** were disappointingly low (20-44%). Experiments which used 1:1 mixtures (entries 4 & 5) performed worst of all (0-6%) with a marked improvement in yield as the ratio moved to either side.

We were encouraged by these results to attempt α -bromination of non-racemic 2-phenylglycine (entry 7). However, the α -bromo acid we isolated after reaction of (*S*)-**127** showed essentially no optical activity; $[\alpha]_D^{20} = 0.73^\circ$ (c=0.15, DCM) [lit. $[\alpha]_D^{20} = -104.6^\circ$ (c=3, ether),¹⁹⁹ $[\alpha]_D^{13.5} = -147.0^\circ$ (c=2, benzene),²⁰⁰] It is clear that nucleophilic attack of bromide on the diazonium species (*S*)-**158** with concomitant loss of the leaving group (N₂ gas) *via* Walden inversion would afford (*R*)-**137** (Scheme 53). The deaminative bromination reaction of α -amino-acids usually proceeds with inversion of configuration at the α -carbon stereocentre,²⁰¹ but where retention of configuration is observed, it is thought to occur *via* neighbouring group participation of the carboxylic acid.²⁰²⁻²⁰⁶ Here, the first nucleophilic attack at the α -carbon of (*S*)-**127** is by the adjacent carboxylate which is said to be lending anchimeric assistance.²⁰⁷ Ring-opening of the severely strained 3-membered α -lactone intermediate **160** should be extremely facile, and as this mechanism involves a second inversion of the stereocentre, the isolated product is now (*S*)-**137**. If either of these two potential mechanisms predominates, our homochiral synthesis would be intact. This racemisation suggests either that both mechanisms operate to a near identical extent, or more

likely in this case, that the phenyl substituent promotes an S_N1 pathway *via* a planar benzylic carbocation **161**.



Scheme 53

Since the completion of our study, Coric *et al.* have reported the synthesis of a number of α -bromo carboxylic acids, with retention of configuration, from the corresponding amino-acids¹⁹⁴ by the Fischer procedure.²⁰⁸ Their report includes the preparation of (R)-137 by treatment of a solution of (R)-phenylglycine in 8 equivalents of 48% HBr and water (2/3 v/v) at 0°C with an aqueous solution containing 3.2 equivalents of NaNO_2 . After 2 hours at 0°C this solution afforded the oily bromo acid, which slowly crystallised on standing, in a yield of 96%.

2-Bromo-2-phenylacetic acid **137** is not available commercially as a single enantiomer but can be resolved by fractional crystallisation of the diastereomeric salts formed with the commercial chiral amine brucine **162** (Figure 18).²⁰⁹ Therefore, we were content to proceed with the further development of this route on racemic material, with the intention to employ optically active bromo acid at a later stage.

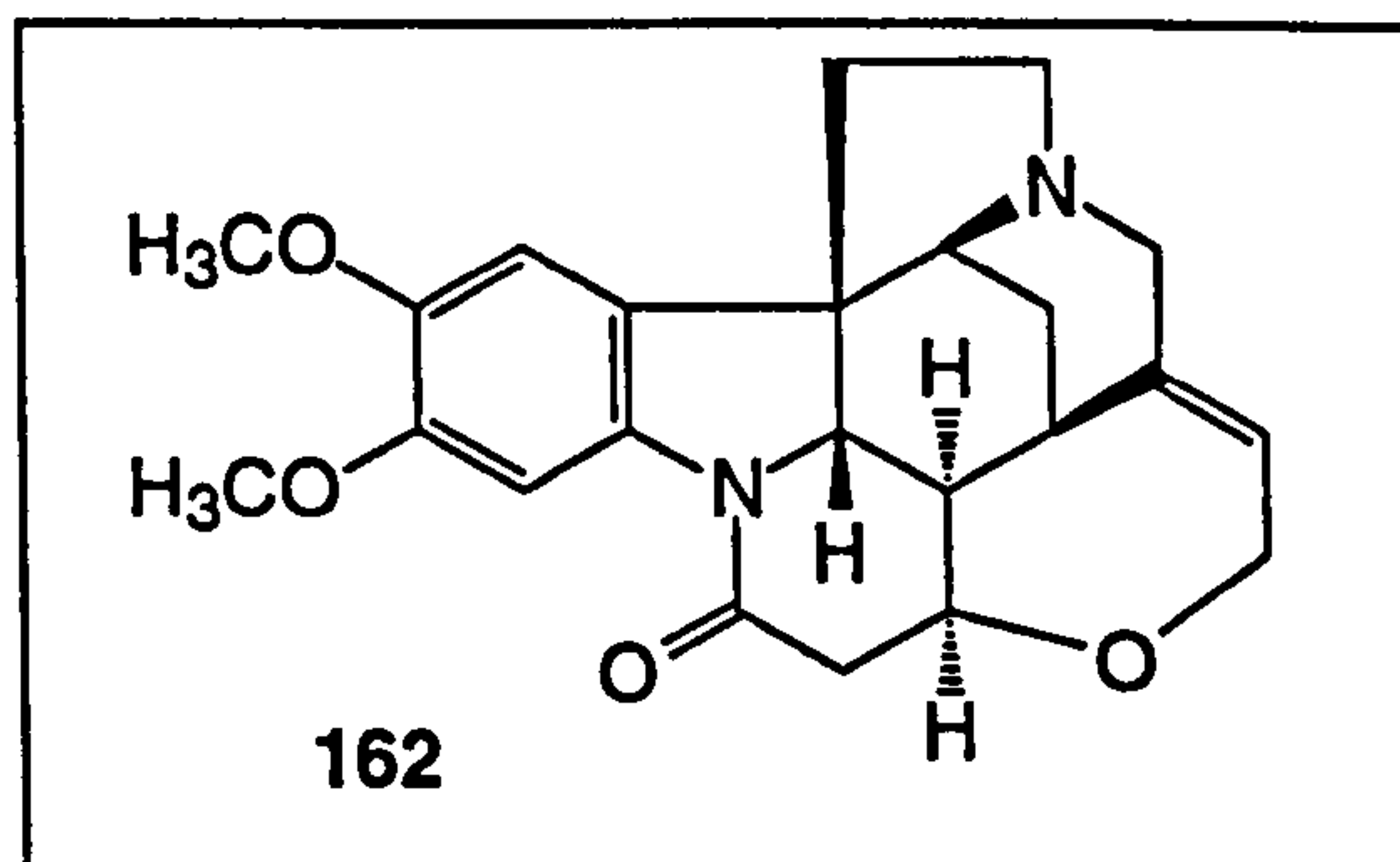
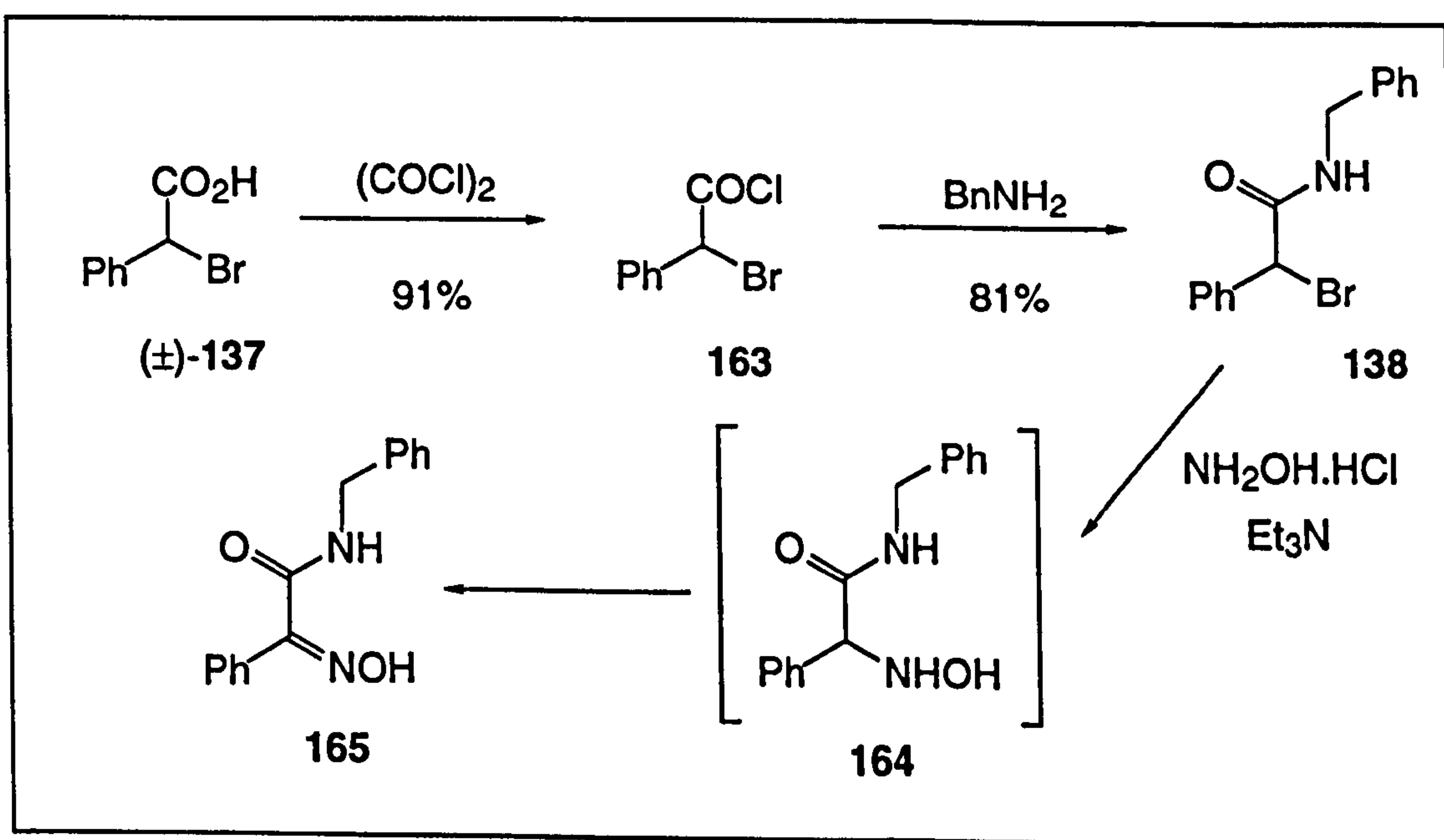


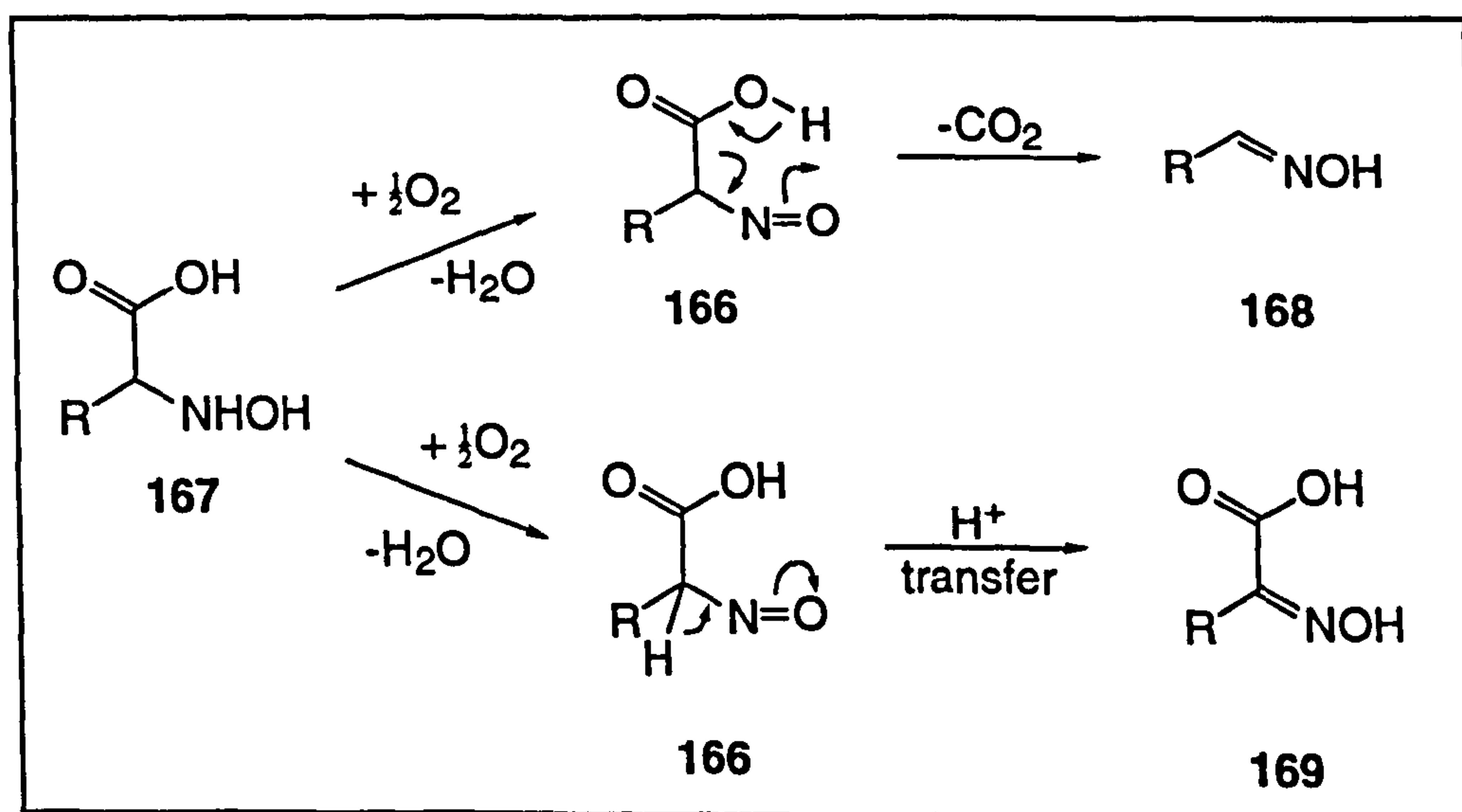
Figure 18



Scheme 54

The racemic α -bromo acid **137** was converted to the acid chloride **163** by treatment with thionyl chloride in DCM at reflux for 18 hours, with purification by vacuum distillation

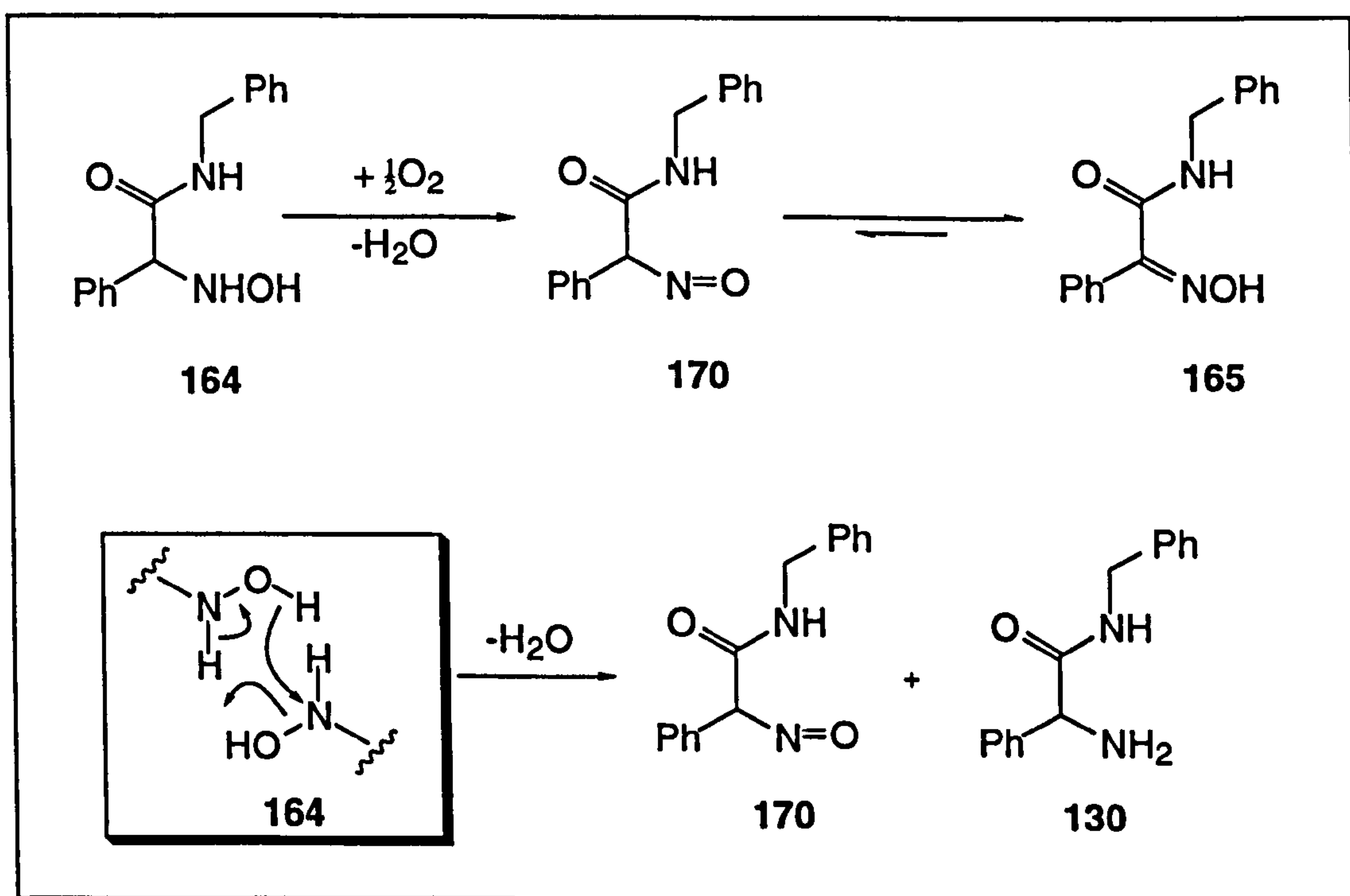
(91%) (Scheme 54). The N-benzyl amide **138** was formed instantaneously on addition of an ether solution of the acid chloride **163** to an ether solution of benzylamine at 0°C. The crude off-white product was isolated by filtration and washed with 1M aqueous HCl and then with ether to give the pure material (81%). We hoped to prepare the hydroxylamino amide **164** by treating the α -bromo amide **138** with hydroxylamine hydrochloride and triethylamine at reflux in anhydrous ethanol. Reaction proceeded to completion but the identity of the isolated product was not immediately apparent. Purification by column chromatography gave a yellow solid that appeared to be a single product but analysis by reverse-phase HPLC (Appendix II) showed this was not the case. The product was in fact the α -oximino amide **165**, present as a mixture of the (*E*)- and (*Z*)-oxime isomers which we were only able to separate and characterise in small quantities using preparative HPLC under carefully developed conditions (Appendix II).



Scheme 55

There is a precedent for the spontaneous conversion of α -hydroxylamino acids to oximino acids²¹⁰ with the corresponding α -nitroso compounds as the proposed intermediate

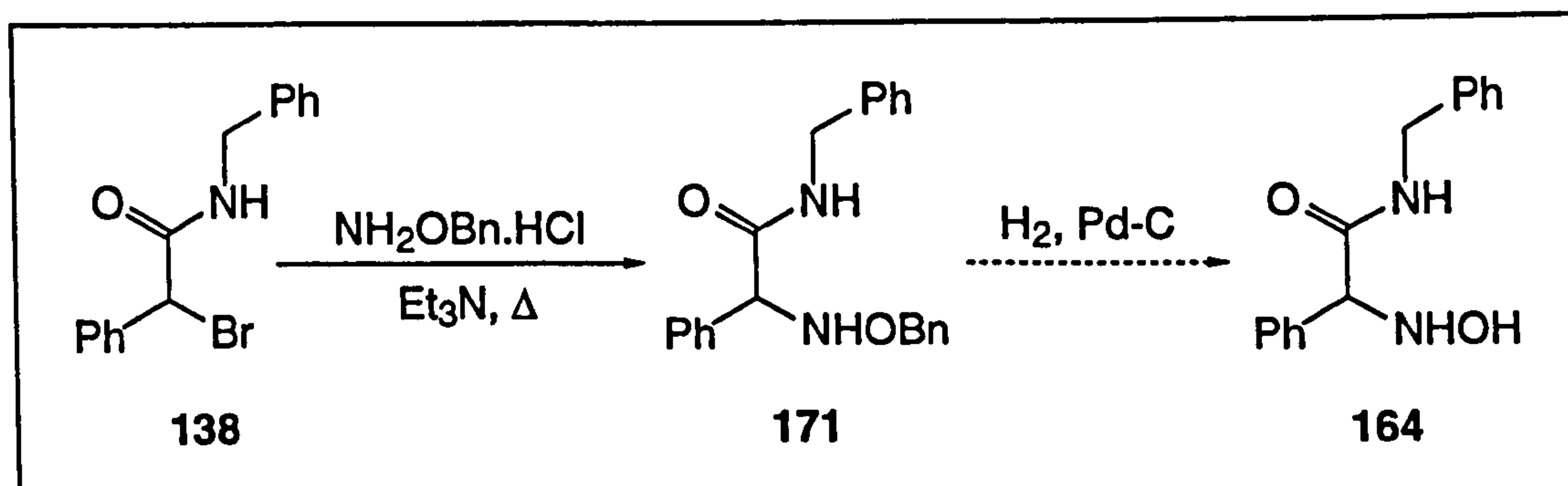
(Scheme 55).²¹¹ It has been suggested that in solution, the α -nitroso acid **166** is formed from the hydroxylamino acid **167** by a pH-dependent oxidative process in which one equivalent of water is eliminated.²¹² Whereas α -nitroso acid **166** can then undergo either decarboxylation to the aldoxime **168** or tautomerisation to the oximino acid **169**, the analogous nitroso amide **170** can only tautomerise to the isolated α -oximino amide **165** (Scheme 56).



Scheme 56

The hydroxylamino acids may also undergo a disproportionation in which two molecules rearrange to the α -nitroso acid and the α -amino acid,^{211,213,214} although this proposal has been questioned.²¹⁵ By analogy, disproportionation of our α -hydroxylamino amide **164** should yield not only the α -oximino amide **165** (in a maximum yield of 50%) but also the α -amino amide **130**. It is perhaps significant that we never observed the amino amide - suggesting a predisposition for formation of the nitroso amide **170** by an oxidative

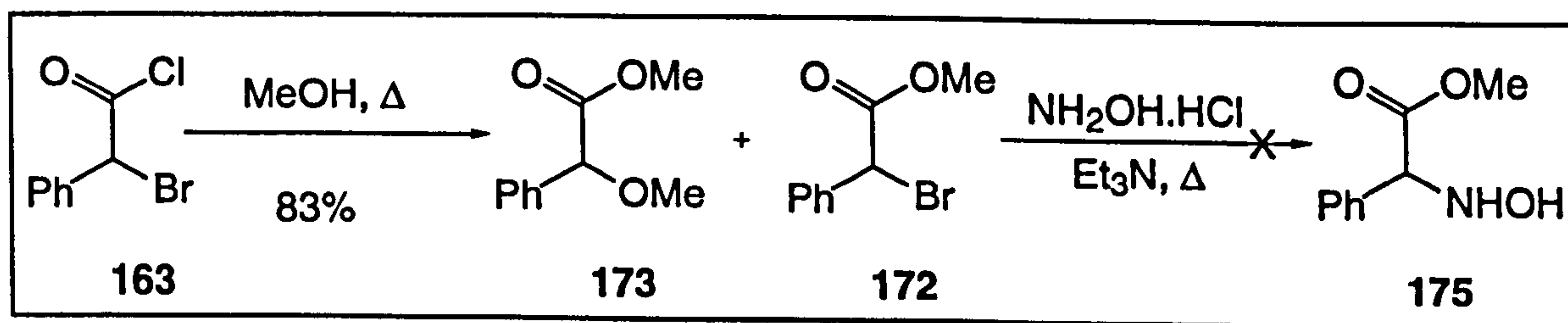
mechanism rather than disproportionation, and thence to the oxime **165**. Attempts to perform the reaction under oxygen-free conditions still produced the oximino amide **165**, suggesting that the excess of hydroxylamine used may be acting as the oxidant, possibly *via* the cyclic mechanism.



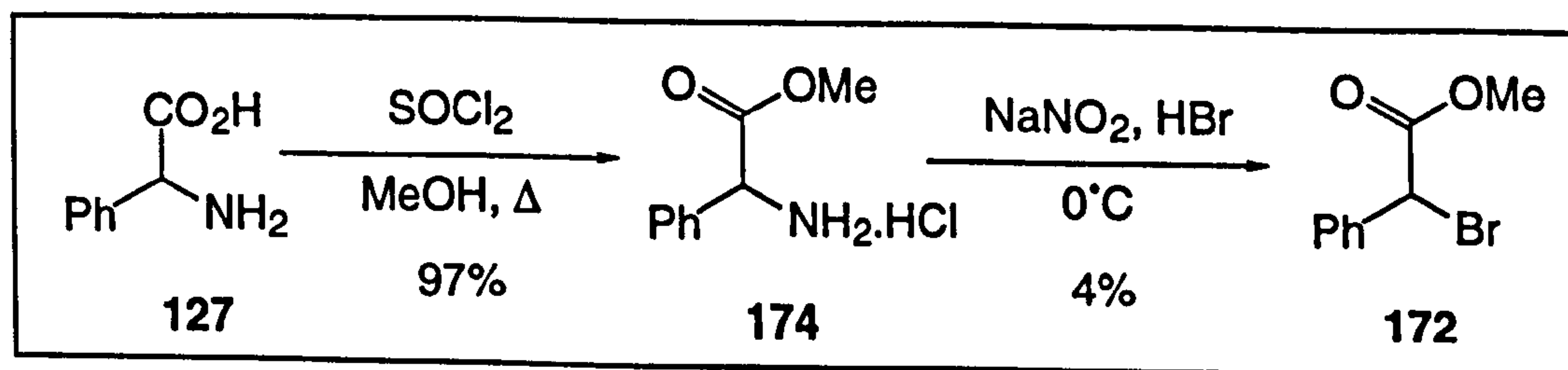
Scheme 57

In order to prevent the formation of the oxime, we decided to prepare the O-benzylhydroxylamino amide **171** (Scheme 57). Whilst many O-alkyl substituents could have prevented the rearrangement, we were mindful that this group would need to be easily removed using as mild conditions as possible to preserve **164** once formed. Thus, O-benzyl protection seemed reasonable, being derived from a commercial hydroxylamine and allowing potential deprotection by hydrogenolysis at ambient temperature and pressure. A solution of the α -bromo amide **138** in DCM was treated with triethylamine and O-benzylhydroxylamine hydrochloride and heated at reflux for 4 hours. After column chromatography, the O-benzylhydroxylamino amide **171** was isolated as a white solid (33%) along with starting material **138** (55%). This reaction proved to be highly capricious, resisting all our attempts to optimise and scale-up beyond this early success into useful quantities of this key intermediate.

The success of the hydroxyamination reactions of α -bromo carboxylic acid esters has been shown to depend to some extent on the choice of ester.^{216,217} In order to find the carboxylic acid derivative most effective for our intended hydroxyamination, we prepared the methyl α -bromo ester **172** (Scheme 58). Heating a solution of the acid chloride **163** at reflux in methanol gave the desired product (83%) with the α -methoxy ester **173** as a trace impurity. We also made a single attempt to prepare ester **172** by the deaminative bromination of the α -amino ester hydrochloride **174** (Scheme 59). Ester **174** was prepared in a 97% yield after treatment of 2-phenylglycine with thionyl chloride in methanol, but the subsequent reaction of **174** with sodium nitrite and HBr at 0°C gave only 4% of the desired α -bromo ester **172**. Attempts to prepare the α -hydroxylamino ester **175** by heating a solution of the α -bromo ester **172** in methanol at reflux with hydroxylamine hydrochloride and triethylamine gave an intractable mixture of products (Scheme 58).

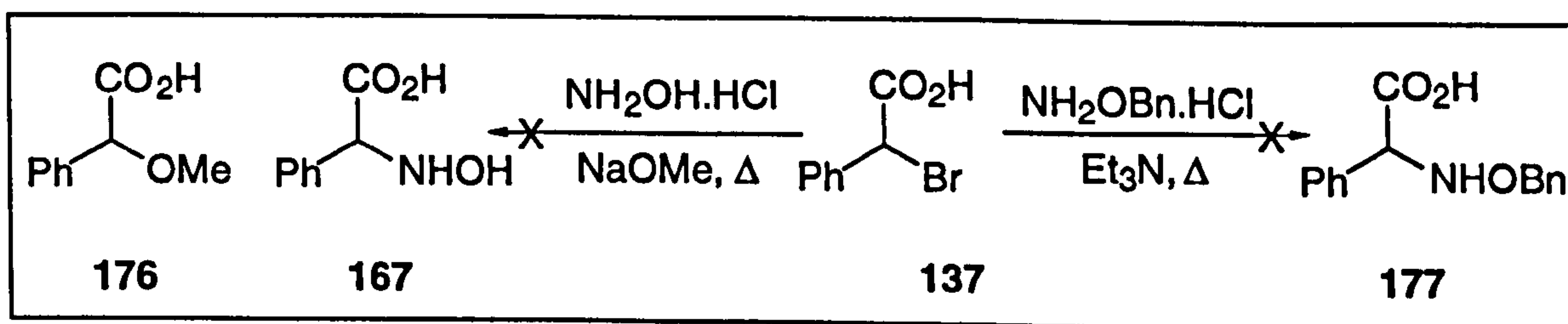


Scheme 58

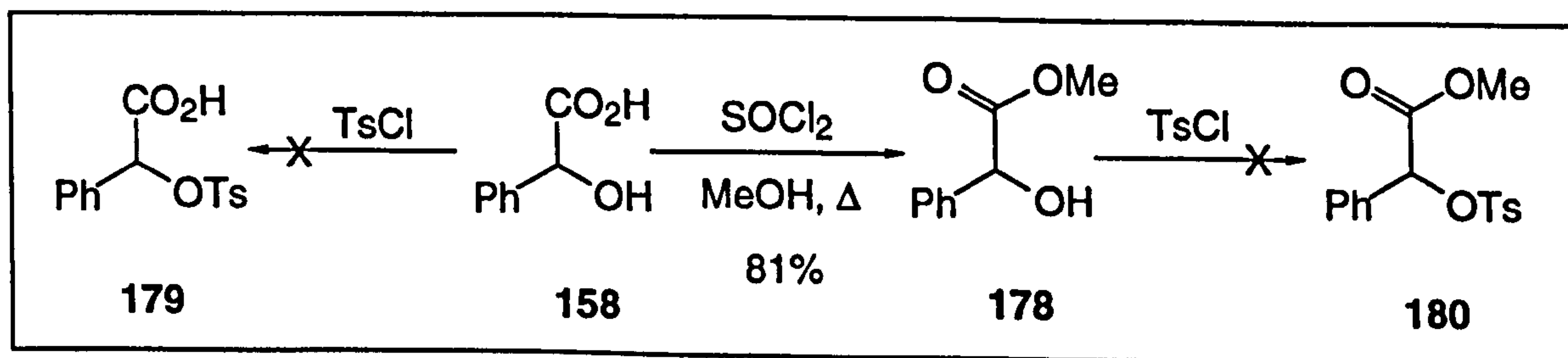


Scheme 59

With the α -bromo acid **137** in hand, we were in a position to further investigate the effect of the acid derivative on the substitution reaction with hydroxylamines (Scheme 60). A mixture of hydroxylamine hydrochloride, sodium methoxide and acid **137** was heated in methanol at reflux for 18 hours but instead of the desired acid **167**, the α -methoxy acid **176** was isolated (21%) after column chromatography. Mindful of the reported instability of the α -hydroxylamino acids towards oxidation, we attempted to synthesise the O-benzylhydroxylamino acid **177**. The α -bromo acid **137** was dissolved in aqueous sodium carbonate and treated with O-benzylhydroxylamine hydrochloride but no reaction was observed after 7 days at reflux. This substitution was also unsuccessful in DCM solution in the presence of triethylamine, despite consumption of the starting material after 18 hours at reflux.



Scheme 60

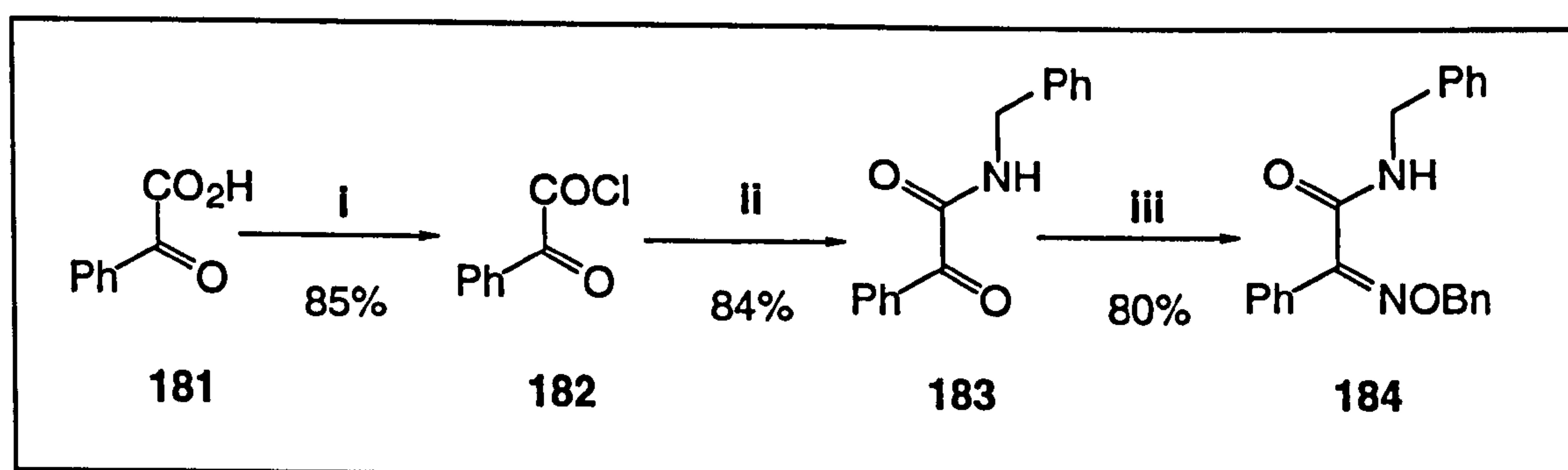


Scheme 61

The use of sulfonate esters as leaving groups is a common strategy to perform a functional group interconversion of the hydroxyl moiety.²¹⁸ Such a strategy has been

employed by Ottenheijm *et al.* in the preparation of α -(O-alkyl)hydroxylamino esters *via* the corresponding α -trifluoromethanesulfonate (triflate) esters,²¹⁹ and by Kolasa in the synthesis of α -(O-benzyl)hydroxylaminoaspartate esters *via* a *p*-toluenesulfonate (tosylate) intermediate.²²⁰ To investigate the effectiveness of a more easily displaced nucleofuge, we proposed to prepare the tosylates of mandelic acid **158** and its methyl ester **178** (Scheme 61). The esterification of **158** was achieved by refluxing with thionyl chloride in methanol solution for 18 hours (81%). However, neither **158** or **178** afforded the desired tosylates **179** and **180** respectively.

2.2.2 Approaches from benzoylformic acid



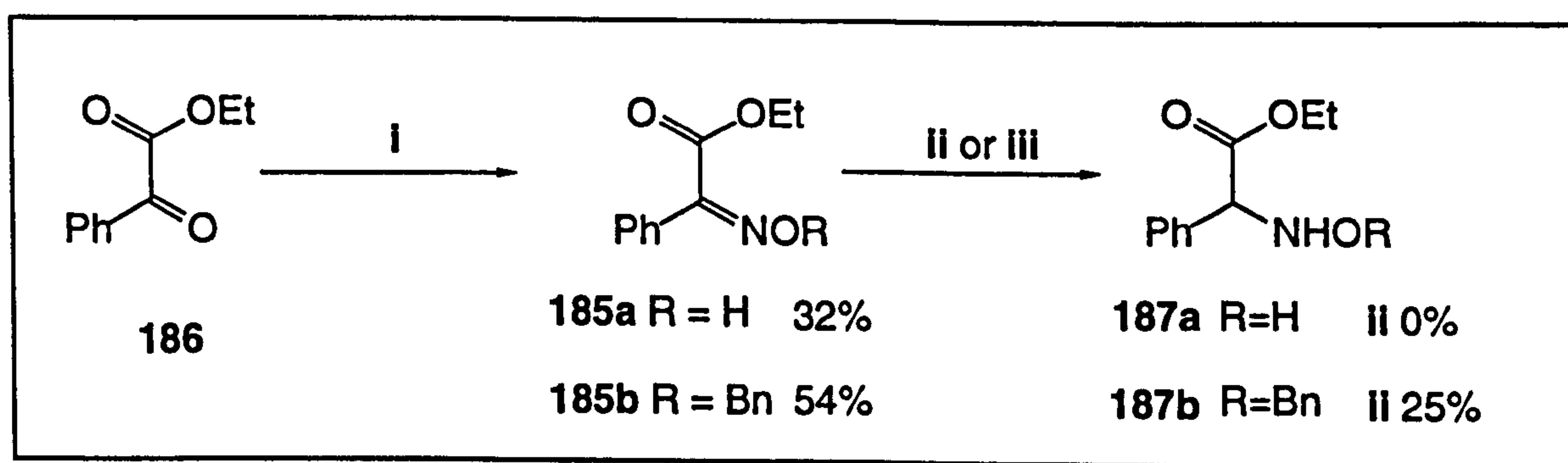
Reagents : i, $(\text{COCl})_2$, DCM, cat. DMF, 20°C, 72h; ii, BnNH_2 , DCM, 0°C; iii, $\text{NH}_2\text{OBn} \cdot \text{HCl}$, Et_3N , EtOH, Δ , 18h.

Scheme 62

The synthesis of O-benzylhydroxylamino amide **171** from the bromo amide **163** remained our most promising route thus far, although the problems of scale-up we had encountered rendered this approach unattractive. It was apparent to us that we could circumvent these difficulties by revision of our synthesis to obtain useful quantities of this

key intermediate *via* reduction of the corresponding oxime, and a synthetic strategy from benzoyl formic acid **181** was thus devised (Scheme 62).

Benzoylformyl chloride **182** was formed from acid **181** after stirring in DCM solution with oxalyl chloride and catalytic DMF for 72 hours. The solvent was removed under vacuum before distillation to yield the product as a yellow oil (85%).²²¹ The N-benzyl ketoamide **183** was formed on dropwise addition of benzoylformyl chloride to a solution of benzylamine and triethylamine (1 equivalent each) in DCM at 0°C. The amide was isolated as an off-white solid (84%) after washing the solution with 2M aqueous HCl followed by drying and evaporating the solvent. The ensuing oximation reaction required heating for 18 hours at reflux of a mixture of **183** with O-benzylhydroxylamine hydrochloride and triethylamine in ethanol. Column chromatography on silica gel afforded the oximino amide **184** as a mixture of *E*- and *Z*- isomers (80%).



Reagents : i, $\text{NH}_2\text{OR} \cdot \text{HCl}$, py, ethanol, Δ , 1h; ii, $\text{BH}_3 \cdot \text{NMe}_3$ (8 equivs.), 7M ethanolic HCl then Na_2CO_3 , DCM.

Scheme 63

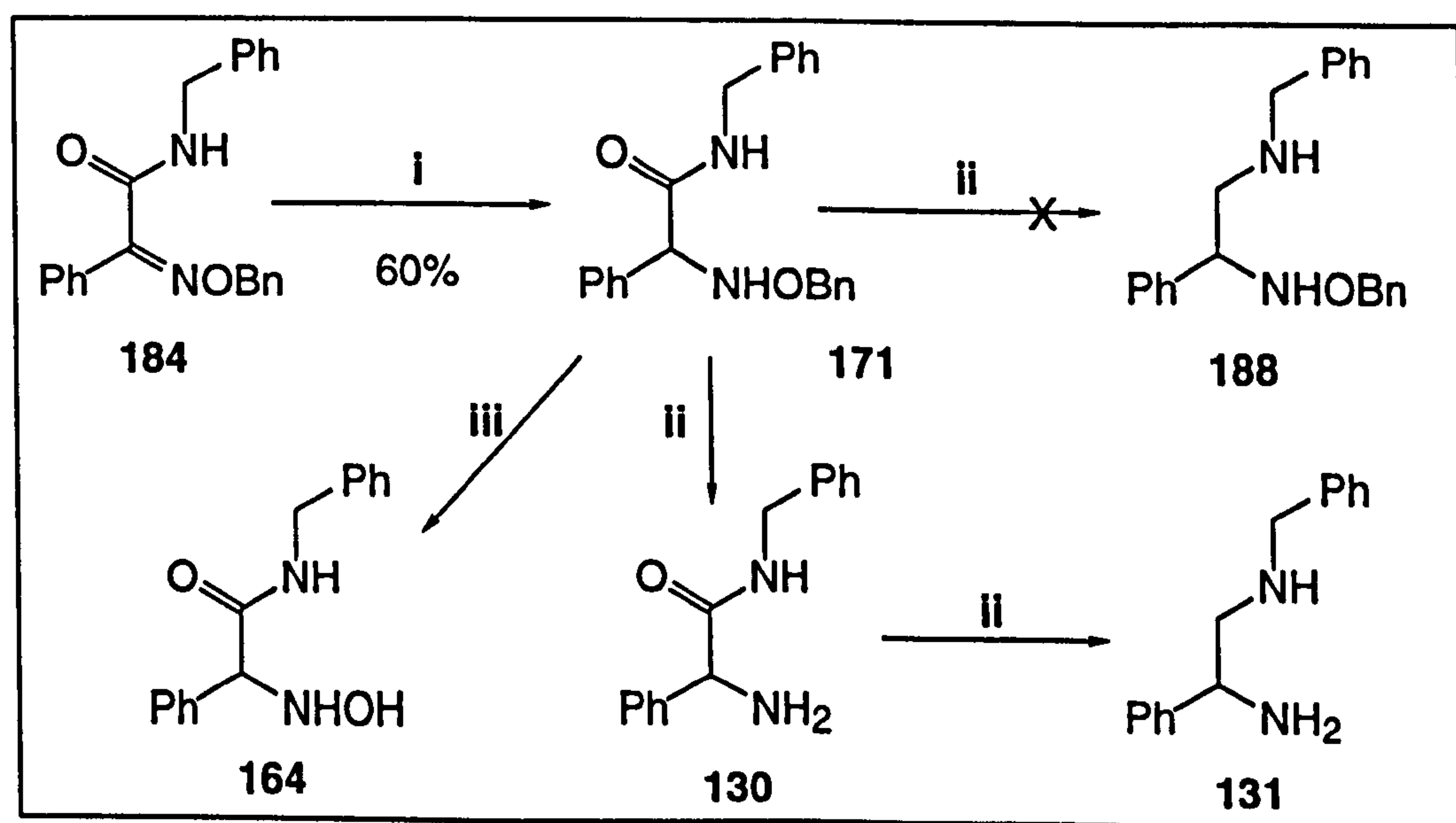
Ottenheijm *et al.* have developed a methodology for the reduction of α -oximino amides and esters to the α -hydroxylamino analogues using borane-amine complexes.^{222,223} As others have found,²²⁴ the use of borane reagents and mild

conditions avoids the over-reduction of the oxime function to the amine that is observed with stronger reducing agents such as lithium aluminium hydride and sodium borohydride.²²⁵ However, there are exceptions; both the α -phenyl oximino ester **185a** and the corresponding N-methyl amide decompose under the acidic conditions required for reduction with either borane-trimethylamine complex ($\text{BH}_3\cdot\text{NMe}_3$) or borane-pyridine complex ($\text{BH}_3\cdot\text{py}$) (Scheme 63).

In order to verify the reduction of oximino acid derivatives, the oximes **185a** and **185b** were prepared from commercial ethyl benzoylformate **186** by heating in ethanol solution with the corresponding hydroxylamine hydrochloride and pyridine at reflux for 1 hour (32% and 54% respectively after chromatography). We confirmed the instability of the OH oxime **185a** under the acidic conditions of $\text{BH}_3\cdot\text{NMe}_3$ reduction, but we successfully reduced the O-benzyl oxime **185b** to the hydroxylamine **187b** in a modest yield of 25% as a mixture with **185b**. A pure sample of **187b** was isolated by preparative HPLC (Appendix II). Encouraged by the reported yield of 95% for $\text{BH}_3\cdot\text{NMe}_3$ reduction of the N-methyl amide analogous to **187b**, this reagent was applied to the reduction of 2-phenyl-2-benzyloximino-N-benzylacetamide **184** (Scheme 64). The amide was taken up in 7M anhydrous ethanolic HCl and treated with 11 equivalents of $\text{BH}_3\cdot\text{NMe}_3$ complex. The solution was stirred at 20°C until all of the amide was consumed, before partitioning between DCM and 1M aqueous NaOH and separation, drying and evaporation of the organic phase to afford the O-benzylhydroxylamino amide **171** as an off-white solid (60%).

We now invoked the methodology that had been developed in our group in connection with the preparation of the 2-imidazoline azomethine ylides **125b**, in which the diamine **131** is prepared by reduction of the amino amide **130** with $\text{BH}_3\cdot\text{THF}$ complex. Thus, a solution of 0.50g of the amide **171** in anhydrous THF was treated dropwise with 7

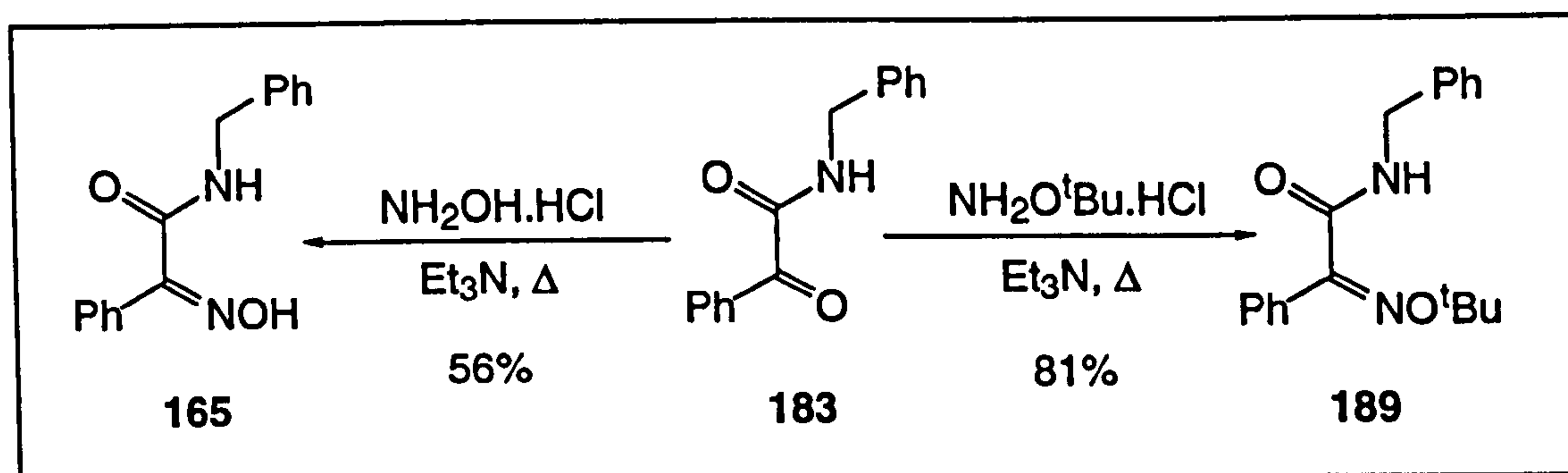
equivalents of $\text{BH}_3\cdot\text{THF}$ complex (as a 1M solution in THF), before heating at reflux to complete consumption of the starting material. Slow addition of 6M aqueous HCl at 25°C was used to cleave the borane-product complex and to decompose excess reagent before extraction into DCM. However, the isolated product was not the desired hydroxylamino amine **188** but 0.45g of a mixture containing the product of amide reduction and concomitant hydroxylamine N–O cleavage **131** and the amino amide **130** (4:1), along with benzyl alcohol. A repeat of this experiment with 4 equivalents of $\text{BH}_3\cdot\text{THF}$ and amide **171** gave no reduction at 20°C, and after a short period at reflux afforded the diamine **131** and the amino amide **130** (2:1), along with benzyl alcohol. Reaction did not proceed at ambient temperature with 1 equivalent of $\text{BH}_3\cdot\text{THF}$, and after 18 hours at reflux, the crude product bore no trace of the diamine **131**. The isolated material proved to contain an approximately equimolar mixture of the hydroxylamino amide **171** and the amino amide **130**, indicating, to our cost, that the N–O reduction occurs before the amide carbonyl is reduced.



Reagents : i, $\text{BH}_3\cdot\text{NMe}_3$, 7M HCl/EtOH, 20°C; ii, $\text{BH}_3\cdot\text{THF}$, THF, Δ , 18h then 6M aq. HCl; iii, H_2 , Pd-C, 20°C, 1 atmos. in gl. AcOH or TFA.

Scheme 64

The O-debenzylation of amino hydroxylamine **188** was to have been carried out by catalytic hydrogenolysis. It was decided to test the feasibility of this deprotection on the amide **171**. We initially studied the reaction of **171** and H₂ at 1 atmos. in the presence of 30mol% of 10% Pd-C at 20°C, a published procedure for O-benzylhydroxamate hydrogenolysis.²²⁶ Unfortunately, this only afforded the N-O cleavage product **130** and benzyl alcohol; this was also the case when the proportion of catalyst was reduced to a more familiar 5mol%. Replacement of the organic solvent with glacial acetic acid or TFA did lead to the desired hydroxylamino amide **164**, but the yields were extremely low (2% and 4%, respectively). As an alternative debenzylation strategy, the amide **171** was refluxed in a solution of conc. HBr/glacial acetic acid but the starting material was recovered unchanged.

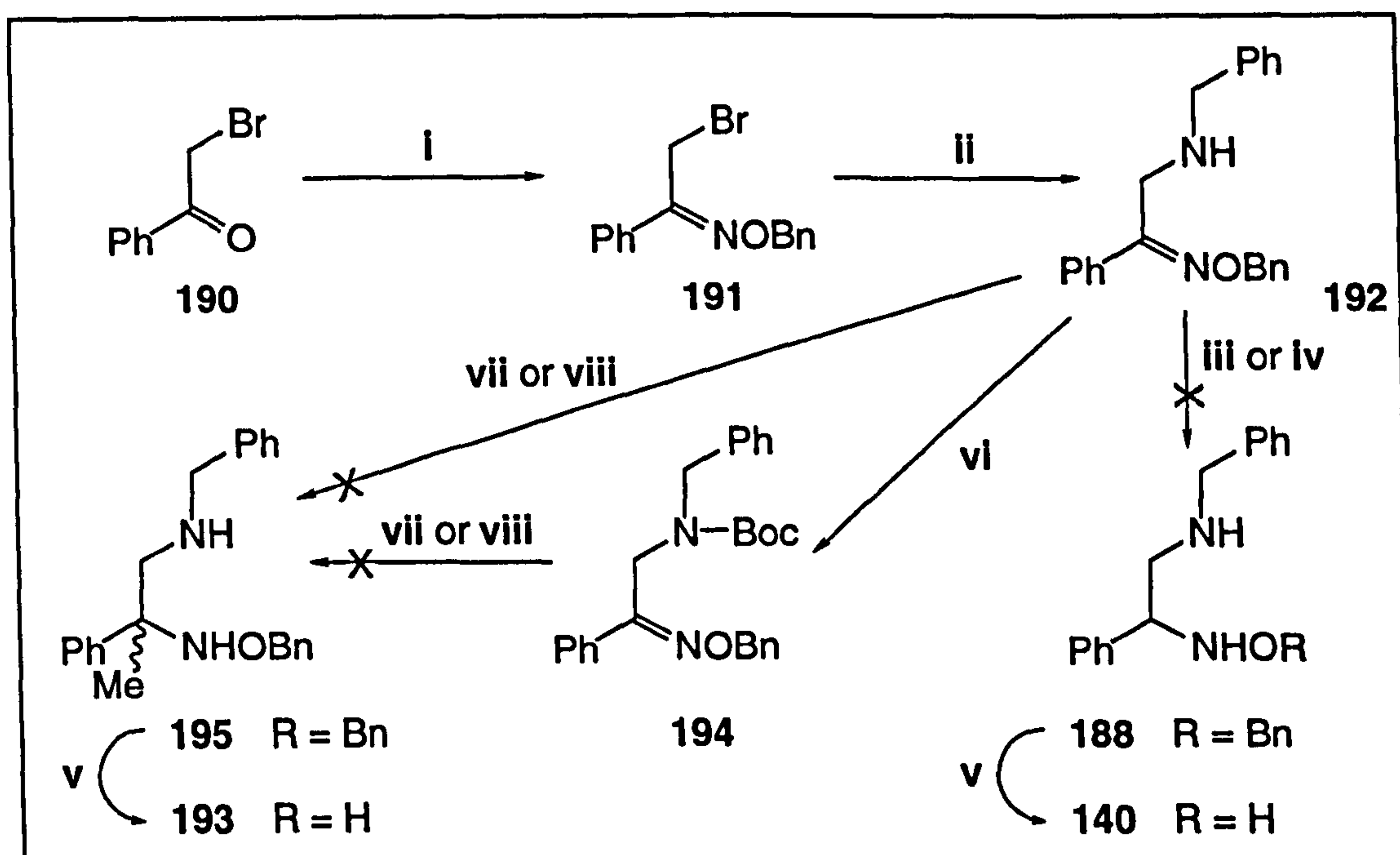


Scheme 65

Our choice of hydroxylamine protecting group was then reconsidered, on the premise that changing the nature of this group might affect the N-O cleavage under carbonyl reduction conditions. The *O*-*tert*-butyloximino amide **189** and the unprotected oximino amide **165** were prepared from a common keto amide starting material **183** (Scheme 65). Ottenheijm has demonstrated the instability of the analogous unprotected oximino ester **185a** under the strongly acidic conditions required for reduction with the borane-amine complexes, and we found that oximino amide **165** was unreactive to BH₃.THF complex or sodium

cyanoborohydride in THF, or aqueous methanol at pH 3-4.²²⁷⁻²²⁹ Our studies on these compounds were concluded when we discovered to our surprise that the *O-tert*-butyl oxime **189** was unreactive to either $\text{BH}_3\cdot\text{NMe}_3$ or sodium cyanoborohydride reduction methodologies, and did not afford the desired hydroxylamine.

2.2.3 Approaches from haloacetophenones



Reagents : i, $\text{NH}_2\text{OBn}\cdot\text{HCl}$, Et_3N , EtOH, Δ , 2h; ii, BnNH_2 , CHCl_3 , Δ , 24h; iii, $\text{BH}_3\cdot\text{NMe}_3$, 7M HCl/EtOH ; iv, NaCNBH_3 , EtOH, pH 3; v, *Proposed reagents* H_2 , 10% Pd-C; vi, Boc_2O , DCM, Et_3N , 20°C, 18h; vii, MeLi, Et_2O , -78°C to 0°C then 2M HCl; viii, $\text{BF}_3\cdot\text{Et}_2\text{O}$, -78°C, 30min then vii.

Scheme 66

We reviewed our synthetic strategy and concluded that the N-benzylamino-functionality we needed could be introduced without recourse to amide reduction. Thus, we resolved to prepare the key nitron precursor hydroxylamino amine **140** via the O-benzyl

analogue **188** (Scheme 66). We reacted 2-bromoacetophenone **190** and O-benzylhydroxylamine hydrochloride in ethanol in the presence of triethylamine to afford the α -bromo oxime **191** which could not be purified further. A chloroform solution of this crude oxime and 2 equivalents of benzylamine was heated at reflux for 18 hours to give the oximino amine **192** after chromatography (50% from **190**). However, we observed no reduction of the oxime **192** with either sodium cyanoborohydride at pH 3 or $\text{BH}_3\cdot\text{NMe}_3$ in ethanolic HCl solution. We then considered alkylation at the oxime carbon by nucleophilic attack of an organometallic reagent,^{230,231} as demonstrated with asymmetric induction by both Moody^{232,233} and Marco.²³⁴ Addition of a methyl group to the oxime carbon of **192** would, after O-debenzylation, afford the hydroxylamino amine **193**. This material is the potential precursor of a nitron with groups of very different steric demand at the nitron α -carbon and so would preserve our synthesis of a facially differentiated 1,3-dipole. Thus, a solution of **192** at -78°C in dry ether under nitrogen was treated with methyllithium (1.6M solution in ether). After 1 hour, the solution was quenched with water and the organic layer separated. However, purification of the crude product mixture by column chromatography afforded none of the desired compound **193**. We reasoned that addition of a Lewis acid may increase the reactivity of the carbon reaction centre of the oxime towards nucleophiles by complexing to the oxime nitrogen *via* its lone pair. However, treatment of the solution of **192** with boron trifluoride etherate ($\text{BF}_3\cdot\text{Et}_2\text{O}$) at -78°C for 15 minutes before adding the methyllithium, and treatment as previously described, still afforded none of the desired material.

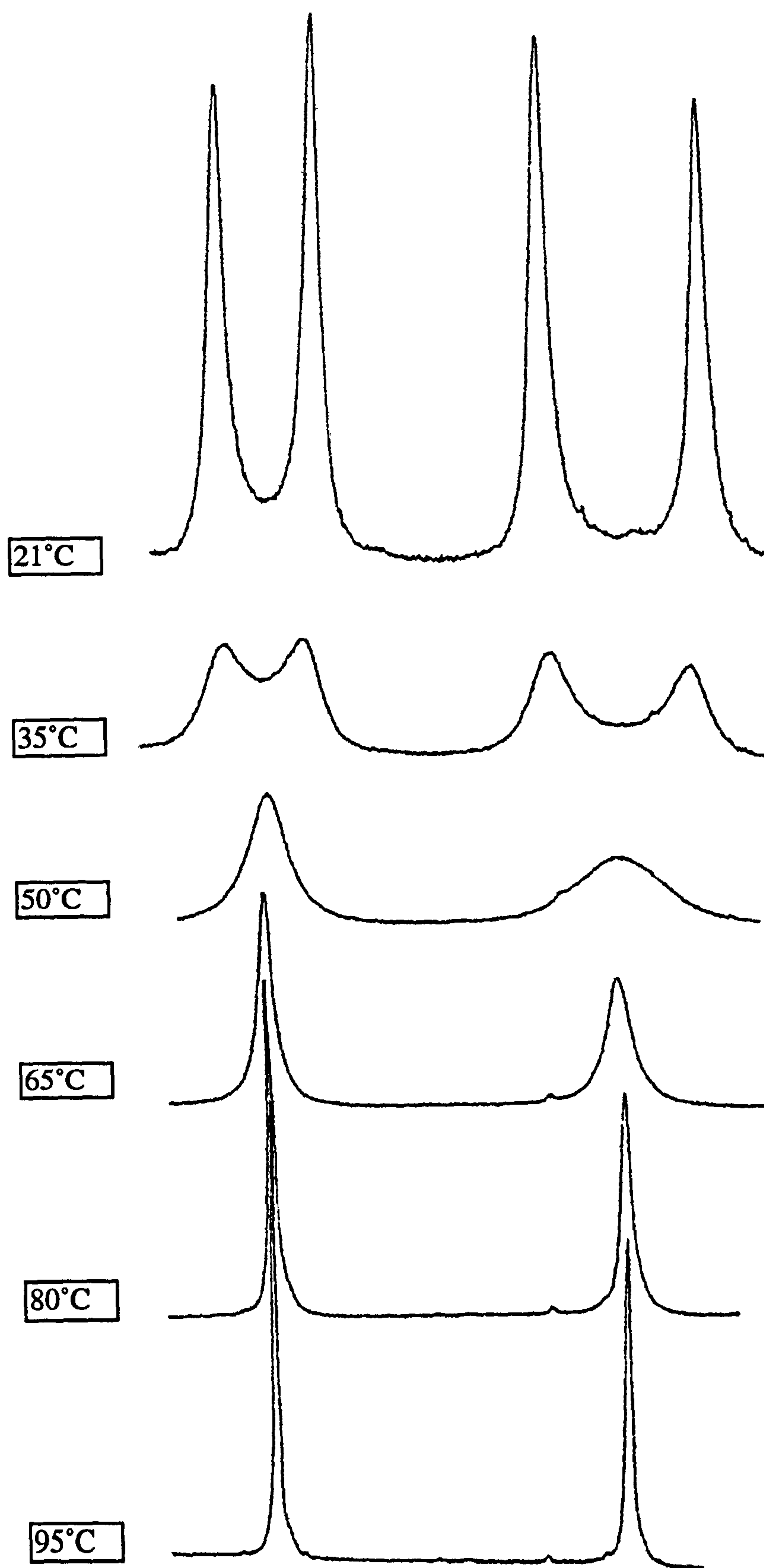
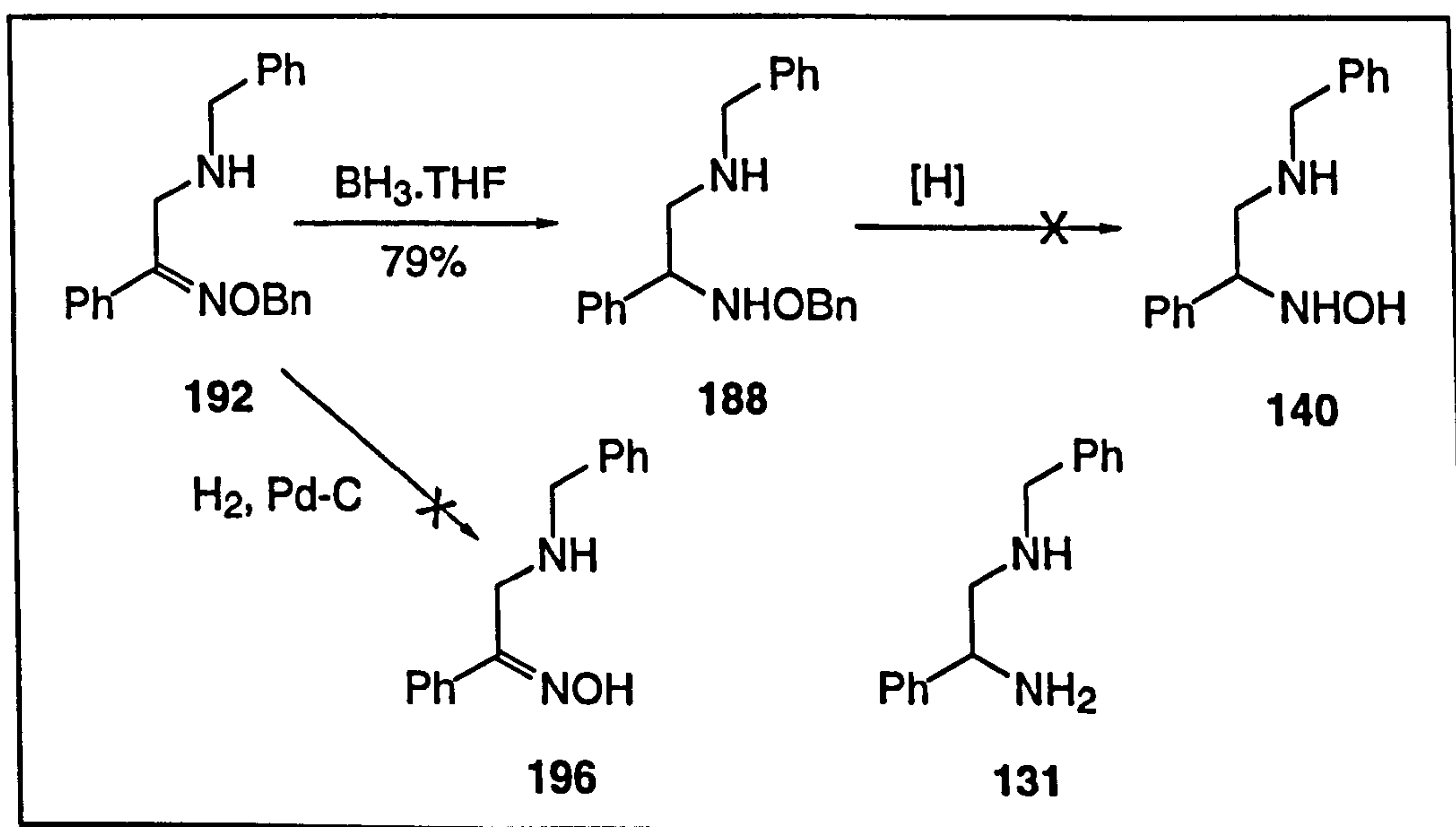


Figure 19 : Collapse of adjacent benzylic CH_2 signals of **194** in variable temperature ^1H NMR spectroscopy.

After these results, the benzylamino moiety of **192** was protected, to avoid any potential interference of the N-benzylamide anion. Stirring a solution of **192** with di-*tert*-butyl dicarbonate (Boc₂O) and Et₃N in DCM solution for 18 hours afforded the carbamate **194** as a white solid (74%) after chromatography. The purified material was found to exist as a pair of *E*- and *Z*-carbamate rotamers at 21°C by ¹H NMR spectroscopy. By variable temperature ¹H NMR spectroscopy in d₆-DMSO, we were able to observe collapse of the doubling of the N-benzyl CH₂ signals above 35°C to give two sharp singlets by 95°C (Figure 19) and so prove the presence of a single compound. A solution of **194** in anhydrous ether at -78°C was treated with 3 equivalents of a 1.6M solution of MeLi in ether but no reaction was observed after 1.5 hours. The solution was warmed to 0°C without change after a further 1.5 hours and, although no starting material remained after warming to 20°C overnight, none of the desired N-Boc-α-methyl hydroxylamine was isolated. A repeat experiment with addition of excess BF₃·Et₂O to the oxime **194** prior to addition of the MeLi solution was also unsuccessful.



Scheme 67

We were able to successfully reduce the oxime **192** under anhydrous conditions with $\text{BH}_3\cdot\text{THF}$ in dry THF (Scheme 67). Inside a few hours, the disappearance of the oxime starting material and the formation of the product-borane complex was easily determined by TLC. This solution was then carefully treated with 2M aqueous HCl and warmed to 60°C until this complexed material disappeared. Neutralisation with 2M aqueous NaOH and extraction into ether gave the desired hydroxylamino amine **188** (79%).

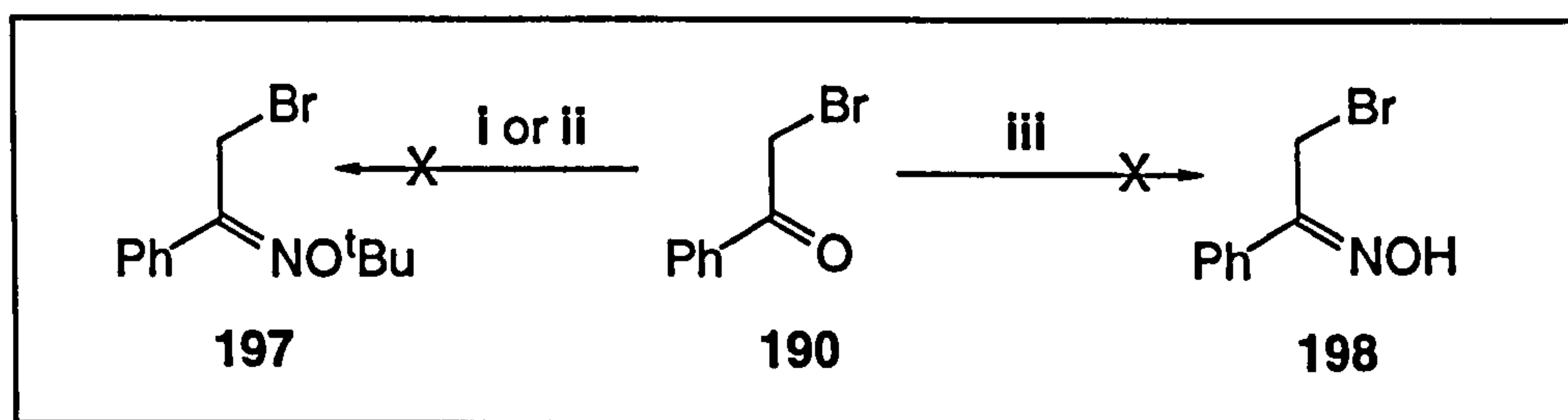
The removal of O-benzyl protecting groups by catalytic hydrogenolysis is often rapid and high-yielding, making it a commonplace strategy in the synthetic literature.²³⁵ Of those reactions of N–O compounds in which O-debenzylation takes place, the palladium-catalysed reactions of O-benzyl hydroxamates^{188,236-238} are the most numerous, but also included is the debenzylation of benzyloxyimidazole.²³⁹ When a solution of the hydroxylamino amine **188** in methanol was stirred with 10% Pd-C under 1atm. of H_2 , the isolated product was not the desired deprotected hydroxylamine **140** but the diamine **131** and benzyl alcohol. Reinhoudt *et al.* have reported high yielding hydrogenolysis reactions of O-benzyl azetidines and azetidinones with palladium catalyst in glacial acetic acid.¹⁸⁸ This result, plus our limited success in the O-debenzylation by hydrogenolysis of the amino amide **171** under acidic conditions, led us to repeat our experiment with glacial acetic acid in place of the organic solvent. However, the isolated products were once again the diamine **131** and benzyl alcohol. The hydrogenolysis of benzyl ethers with Raney Nickel catalyst at ambient temperature and pressure has been reported²⁴⁰ but, after 72 hours under such conditions, the hydroxylamine **188** was recovered unchanged.

Following precedent for cleavage of benzylic alcohols and amines by catalytic transfer hydrogenolysis,²⁴¹⁻²⁴³ hydroxylamino amine **188** was heated at reflux in methanol with 10% Pd-C and ammonium formate. After 18 hours, the reaction was halted

but the isolated material was an intractable mixture of products. Brown *et al.* have generated N-hydroxypurine derivatives from the corresponding benzyloxypurines by heating in a solution of conc. HBr in glacial acetic acid.²⁴⁴ We found that the hydroxylamino amine **188** was retrieved unreacted after 18 hours at reflux in 30% HBr in glacial acetic acid. In a more exotic example, the O-benzylhydroxylamino phosphonic and phosphinic acids of Elhaddadi *et al.* are deprotected without N–O cleavage using boron tris(trifluoroacetate), B(TFA)₃.²⁴⁵ This reagent was prepared by treatment of a solution of distilled TFA in anhydrous DCM with boron tribromide under an atmosphere of nitrogen. A white precipitate of B(TFA)₃ formed instantaneously and was isolated by removal of the solvents *in vacuo*, before it was added to a solution of **188** in TFA and the mixture stirred under nitrogen for 18 hours. The solution was diluted with MeOH before basifying with aqueous NaOH (2M) but only the unchanged starting material **188** was recovered. We were somewhat consoled by the fact that many other researchers have found O-benzylhydroxylamines to be susceptible to N–O cleavage under catalytic hydrogenolysis conditions.^{246,247} Interestingly, Corey *et al.* have reported oxime O-debenzylation by Pd-catalysed hydrogenolysis²⁴⁸ but, using this method, the oxime **192** afforded a 1:1 mixture of the diamine **131** and benzyl alcohol rather than the desired oxime **196**. On balance, we decided that the search for an alternative hydroxylamine protection strategy was our most judicious option.

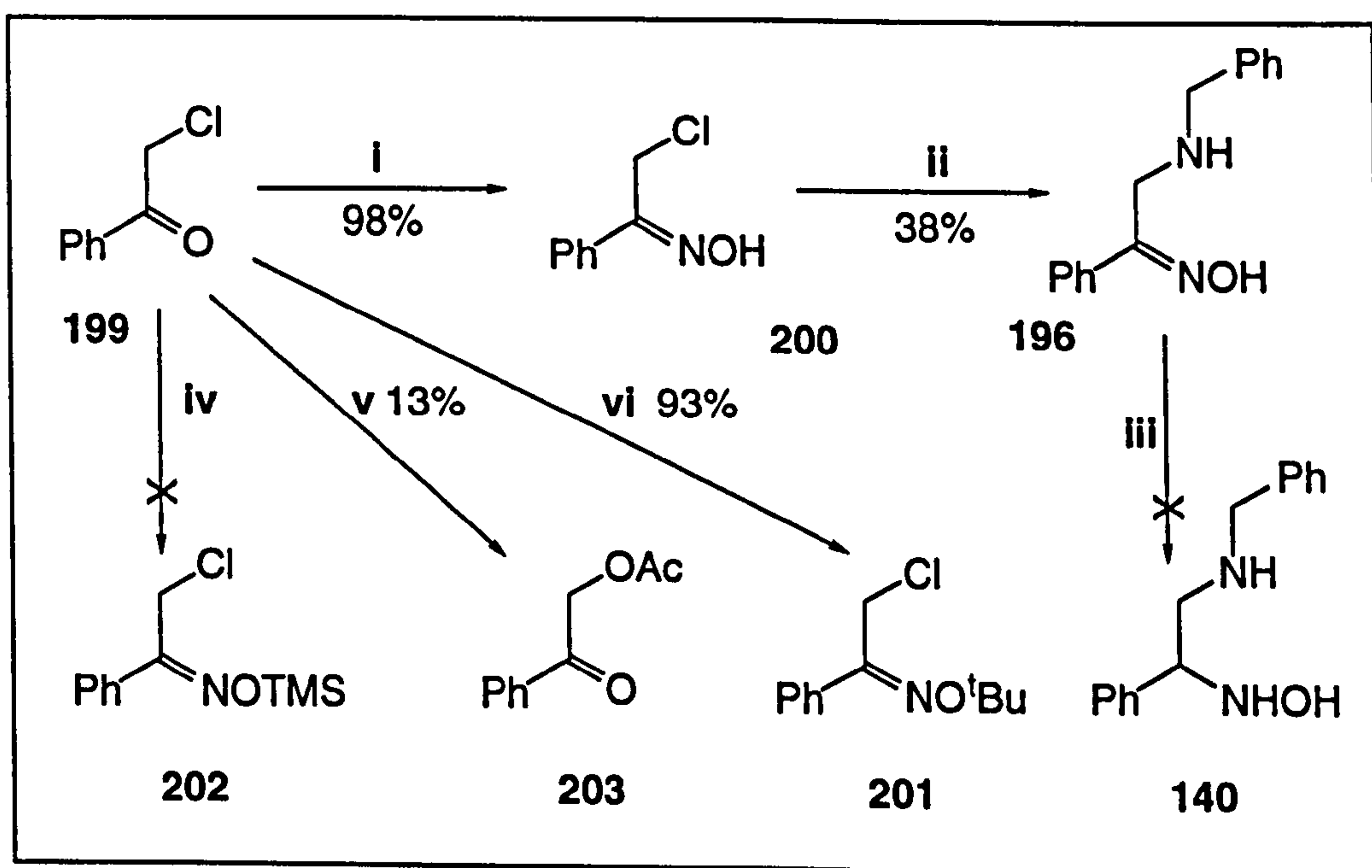
To this end, the α -bromo-O-*tert*-butyl oxime **197** became our next target, offering, after elaboration, a potentially facile non-hydrogenolytic dealkylation to afford the hydroxylamine **140** (Scheme 68). Unfortunately, we were unable to prepare this oxime from 2-bromoacetophenone **190** by conditions developed during the preparation of **192** with O-*tert*-butylhydroxylamine hydrochloride and either triethylamine in refluxing ethanol

or in aqueous sodium acetate at 20°C or 50°C. Similarly, we were unable to prepare the analogous unprotected oxime **198** under these conditions.



Reagents : i, NH₂O^tBu.HCl, Et₃N, EtOH, Δ, 18h; ii, NH₂O^tBu.HCl, NaOAc, H₂O, 50°C or 25°C, 18h; iii, NH₂OH.HCl, Et₃N, EtOH, Δ, 48h.

Scheme 68



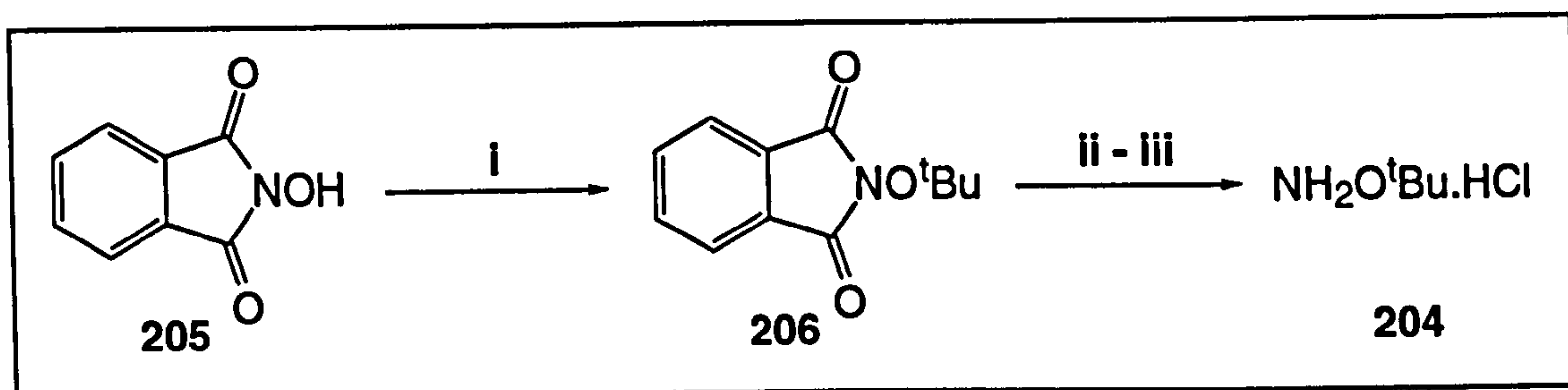
Reagents : i, NH₂OH.HCl, NaOAc, MeOH, 18h, 20°C; ii, BnNH₂, CHCl₃, Δ iii BH₃.THF, THF then 6M aq. HCl, 24h at 20°C (or 4h at 50°C); iv, NH₂OTMS, 4Å sieves, dry CHCl₃, 20°C, 36h; v, NaOAc, EtOH, Δ, 18h; vi, as i with NH₂O^tBu.HCl.

Scheme 69

Our difficulties with α -bromo oximes led us to investigate their α -chloro analogues. Much work has been done on the preparation of α -chloro oximes as precursors to nitrosoalkenes.^{249,250} By the method of Denmark and Dappen,²⁴⁹ a methanol solution of 2-chloroacetophenone **199** was treated with 1.5 equivalents each of hydroxylamine hydrochloride and potassium acetate but returned none of the desired oxime **200**. In contrast, an alternative procedure from these researchers using 1.5 equivalents of both hydroxylamine hydrochloride and sodium acetate²⁴⁹ furnished the desired chloro oxime **200** in a near quantitative yield (98%) (Scheme 69). Subsequent amination of oxime **200** proceeded in a moderate yield (38%) by the method developed for the synthesis of the *O*-benzyl oxime **192**, with benzylamine in chloroform. However, the oximino amine **196** was not reduced by the $\text{BH}_3\cdot\text{THF}$ complex after 24 hours at 20°C nor after 4 hours at 50°C.

Similarly, reaction of **199** with *O*-*tert*-butylhydroxylamine hydrochloride and sodium acetate gave the desired chloro oxime **201** in excellent yield (93%). Optimisation studies showed that scale did not seem to adversely affect the isolated yield of **201**, an experiment using 0.56g of **199** proceeding with a yield of 79%, with 82% from 1.12g and 87% from 2.80g. The alternative reaction conditions using potassium acetate in glacial acetic acid were successful, but the yields were significantly lower (49% and 68% in two attempts). We made a single attempt to prepare the *O*-trimethylsilyl chloro oxime **202** as an alternative protecting-group strategy by a third method from Denmark's work using *O*-trimethylsilylhydroxylamine,²⁵¹ but observed no reaction after 36 hours. During our optimisation, we investigated the effect of prolonged exposure of 2-chloroacetophenone to the oximation conditions. Thus, after 18 hours at reflux of a solution of 2-chloroacetophenone in ethanol with sodium acetate, we isolated the acetate adduct **203**, but only in 13% yield. Our findings here support our contention that this side product will not

significantly affect our isolated yield of oxime **201** in the room temperature oximation reaction.



Reagents : i, AcO^tBu, 60% HClO₄, 1,4-dioxane 20°C, 18h then aq. NaHCO₃; ii, NH₂NH₂.H₂O, aq. EtOH, Δ, 1h then aq. Na₂CO₃; iii, gaseous HCl.

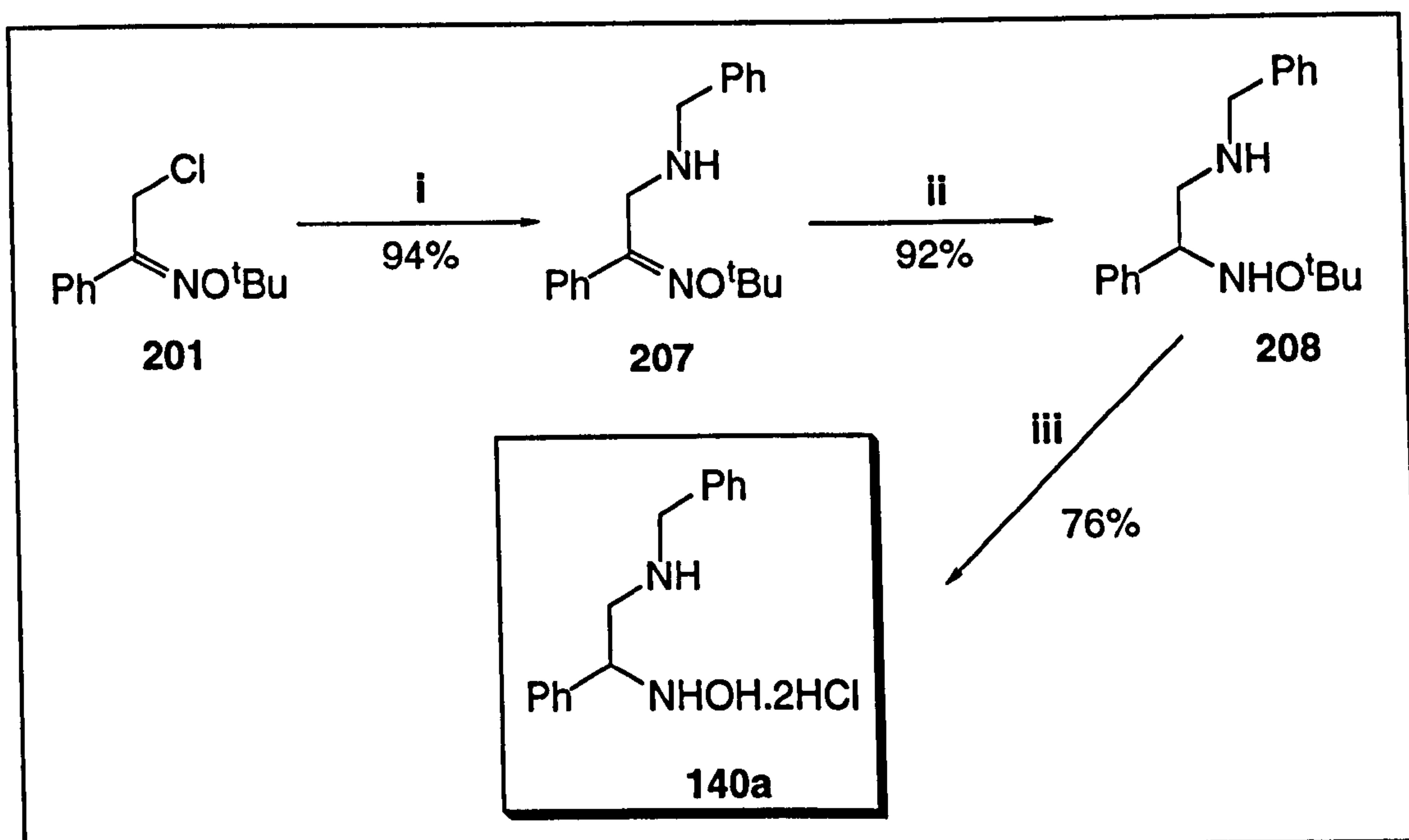
Scheme 70

The prohibitive cost of O-*tert*-butylhydroxylamine hydrochloride **204** (£21.40/g) encouraged us to prepare our own supplies using a literature synthesis from N-hydroxyphthalimide **205** (Scheme 70).^{252,253} This method is reported to afford a 99% yield of the O-alkylated product **206** with 10 equivalents of *tert*-butyl acetate and catalytic perchloric acid in 1,4-dioxane.²⁵² We found that this could be reduced to 4 equivalents with no loss of yield of a product that required only to be washed with hexane for analytical purity. The *tert*-butyl acetate was prepared by esterification of acetyl chloride with *tert*-butanol in the presence of N,N-dimethylaniline (60% in our hands after distillation).²⁵⁴ Whilst this synthesis was suited to a large scale, we found the commercial ester to be of sufficient purity and without deterrent cost once we had developed a route to the phthalimide intermediate **206** with more modest demands of this ester.

Cleavage of the O-*tert*-butylphthalimide **206** with hydrazine monohydrate was performed according to the method of Chimiak and Kolasa.²⁵³ Reaction had proceeded to completion after 3 hours at reflux, and so the solution was cooled and treated with 5%

aqueous Na_2CO_3 solution. After 30 minutes at 20°C , this solution was extracted with ether and the dried organic phase was treated with dry gaseous HCl . Initial experiments in ethanol or *tert*-butanol gave identical, modest yields of *O-tert*-butylhydroxylamine hydrochloride **204** (52%) along with copious amounts of phthalhydrazide which precipitated from the aqueous phase on standing. Ethanol later proved to be our best solvent with a yield of 77%, although we have not matched the literature reports of 85%. Previous attempts to prepare the phthalimide **206** in a Mitsunobu-type reaction by the treatment of **205** with *tert*-butanol, triphenyl phosphine and diethyl azodicarboxylate afforded none of the desired product. Alkylation of **205** with *tert*-butyl iodide in DMF and triethylamine was also unsuccessful.

The subsequent substitution of the chloride of *O-tert*-butyl oxime **201** proceeded most efficiently with 2 equivalents of benzylamine in DMF at 20°C (Scheme 71). Whilst removal of the high-boiling solvent is tedious, the compensation is a high yield of the oximino amine **207** (94%). Less effective experiments included heating at reflux in chloroform (for a 17% yield of **207** with 60% recovered **201**), THF (63%), toluene (73% of **207** with 12% **201**) and an experiment with no solvent and 30 equivalents of benzylamine (71%). The reduction procedure used 4 equivalents of BH_3 .THF complex, added to a dry THF solution of the oximino amine **207** as a 1M solution at 0°C under nitrogen. Even on a multi-gram scale, the oximino amine was consumed in only a few hours at 20°C , and careful addition of 6M aqueous HCl at 0°C freed the desired hydroxylamino amine **208** from its complex with borane. The solution was basified and extracted with ether, before drying and evaporation of the solvent and purification of the residue by column chromatography.



Reagents : i, BnNH₂, DMF, 20°C, 18h; ii, BH₃.THF, THF, 20°C, 1h then 6M aq. HCl, 20°C, 1h;

iii, c. HCl, MeOH, Δ, 18h *or* c.H₂SO₄, MeOH 30 min then gaseous HCl, 1h.

Scheme 71

The susceptibility of the BH₃.THF complex to hydrolysis meant that moisture had to be excluded from these experiments, but we also found that older samples of this complex contained THF-related contaminants. Kollonitsch discovered that THF is subject to ring-opening by borane, such that tributyl borate had formed in the borane-THF sample over time,²⁵⁵ and we also observed this during the reduction of oxime 207. Consequently, one of the contaminants we had observed was butan-1-ol formed in the acid hydrolysis step of the reduction and derived from tributyl borate. Similarly, we isolated a second impurity which we identified as 4-chlorobutan-1-ol, clearly formed by chloride-induced ring-opening of THF during the hydrolysis step with HCl. Both impurities were avoided by the use of a fresh solution of the complex with storage in the cold between uses, and minimal hydrolysis times with immediate work-up on completion. In early experiments where excessive amounts of these ring-cleavage products had formed, silica column chromatography proved

to be ineffective, co-eluting these impurities with the product. It was, therefore, necessary in these cases to distill the crude reaction mixture to remove the alcohols, before performing a final chromatographic purification leading to a seriously diminished yield of hydroxylamino amine **208**.

Our initial protocol to deprotect the *O-tert*-butylhydroxylamino amine **208** was treatment with TFA, but this only led to isolation of the TFA salt of our starting material. Literature precedent for *O-tert*-butyl ether cleavage^{256,257} led us to try hydrolysis with TFA and anisole, but no desired material was returned. This was followed by attempts with trimethylsilyl iodide (TMSI) - a reagent that is reported to afford instantaneous cleavage of benzyl and *tert*-butyl ethers^{258,259} but which was unfruitful here. Our first successful deprotection of **208** was observed after prolonged heating at reflux in a solution of equal volumes of conc. HCl and methanol. On completion, the mixture was cooled then basified with 2M aqueous NaOH and extracted with ether. From this solution was obtained a yellow-green gum, consistent with the desired hydroxylamino amine by NMR spectroscopy, but showing signs of decomposition in less than 7 days in CDCl₃ solution. Attempts to purify this oily amine by distillation or column chromatography also seemed to induce decomposition. We were eventually able to effect purification and isolation after treatment of the free base in DCM solution with ethereal HCl to afford the pure dihydrochloride salt **140a**.

Optimisation studies led us to deprotection with conc. H₂SO₄. Dropwise addition of this acid to a methanol solution of **208** gave an immediate and significant exotherm. The deep brown solution so produced was internally and externally cooled with ice during basification with 6M aqueous NaOH at first and later solid NaOH, before extraction with DCM and drying of the extracts over anhydrous MgSO₄. The solution was filtered and then

treated with dry HCl gas for 1 hour. The dihydrochloride salt **140a** slowly precipitated from the solution on standing and was removed by filtration before drying under vacuum.

Occasionally, we have encountered difficulties in the purification of the salt, especially if the *O-tert*-butyl amine **208** was not pure or if the DCM solution of the free base was not dried thoroughly over anhydrous MgSO_4 . Usually, however, the material isolated in this way was a white amorphous solid, with high purity by NMR spectroscopy, in yields of up to 76%. Purity was also assessed by a reverse-phase HPLC method (Appendix II), using an aqueous acetonitrile eluent. A gradient elution system was employed (i.e. of decreasing solvent polarity with time), which initially eluted with a 10% solution of acetonitrile in water with 0.1% TFA (solution A) and a flow rate of eluent of $1\text{cm}^3/\text{min}$. A 90% solution of acetonitrile in water with 0.1% TFA (solution B) was introduced such that after 15 minutes of run time, the ratio of A:B was 1:9 by volume which eluted for a further 10 minutes (Figure 20).

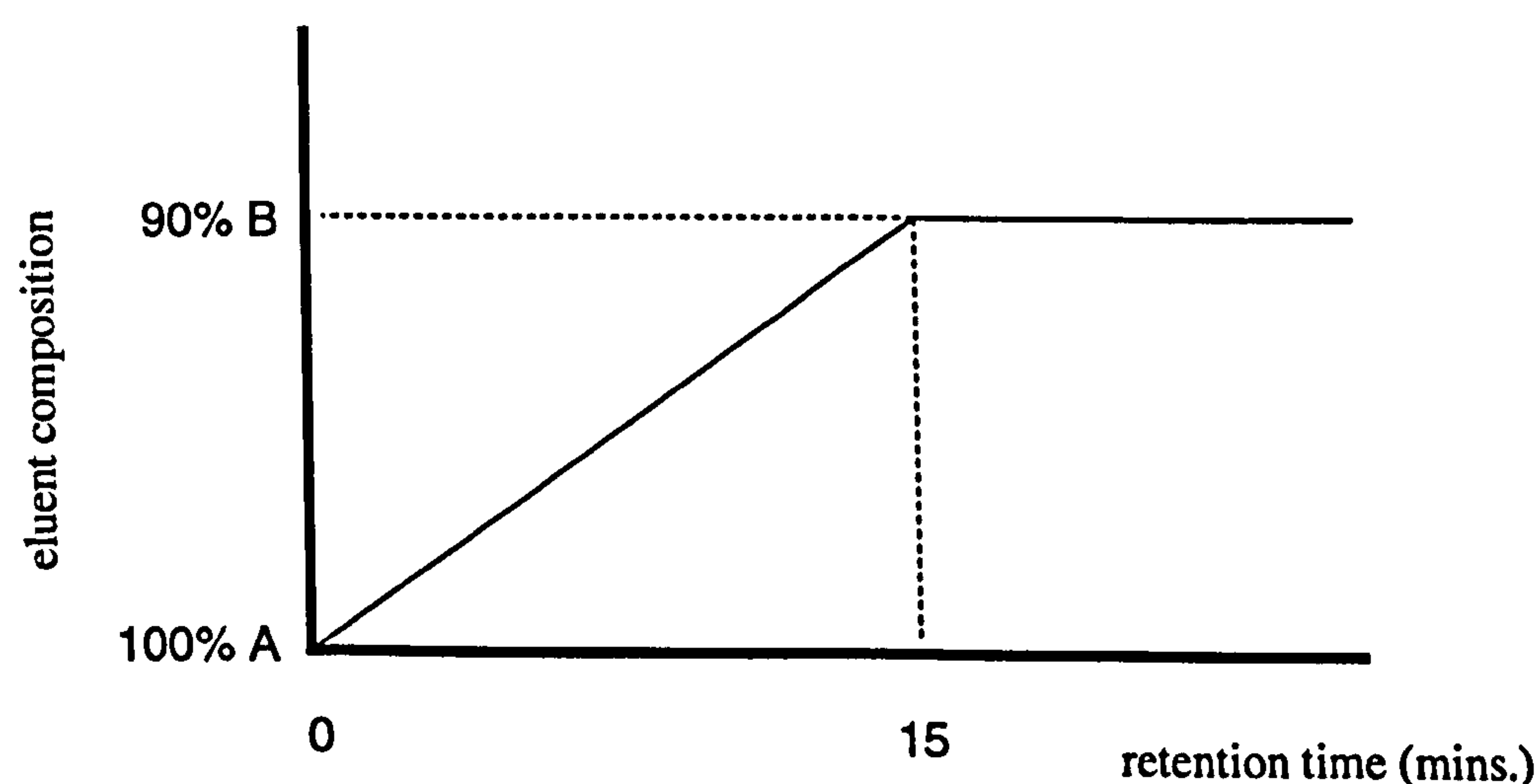


Figure 20 : HPLC eluent gradient as used for analysis of **140a.**

This system eluted the hydroxylamino amine salt **140a** with a retention time of approximately 10 minutes, and in this way we were able to show that the purity of the

isolated material was increased significantly by trituration with a little cold DCM (Figure 21). This system used a UV detector at a wavelength of 258nm, where most organic compounds absorb strongly. However, we were mindful of the fact that the relative absorption of a mixture of organic compounds does not always relate to the relative concentrations on account of their different UV absorption coefficients. We did not seek to make our analysis quantitative, but found it to be a useful guide in our development of subsequent cycloaddition reactions.

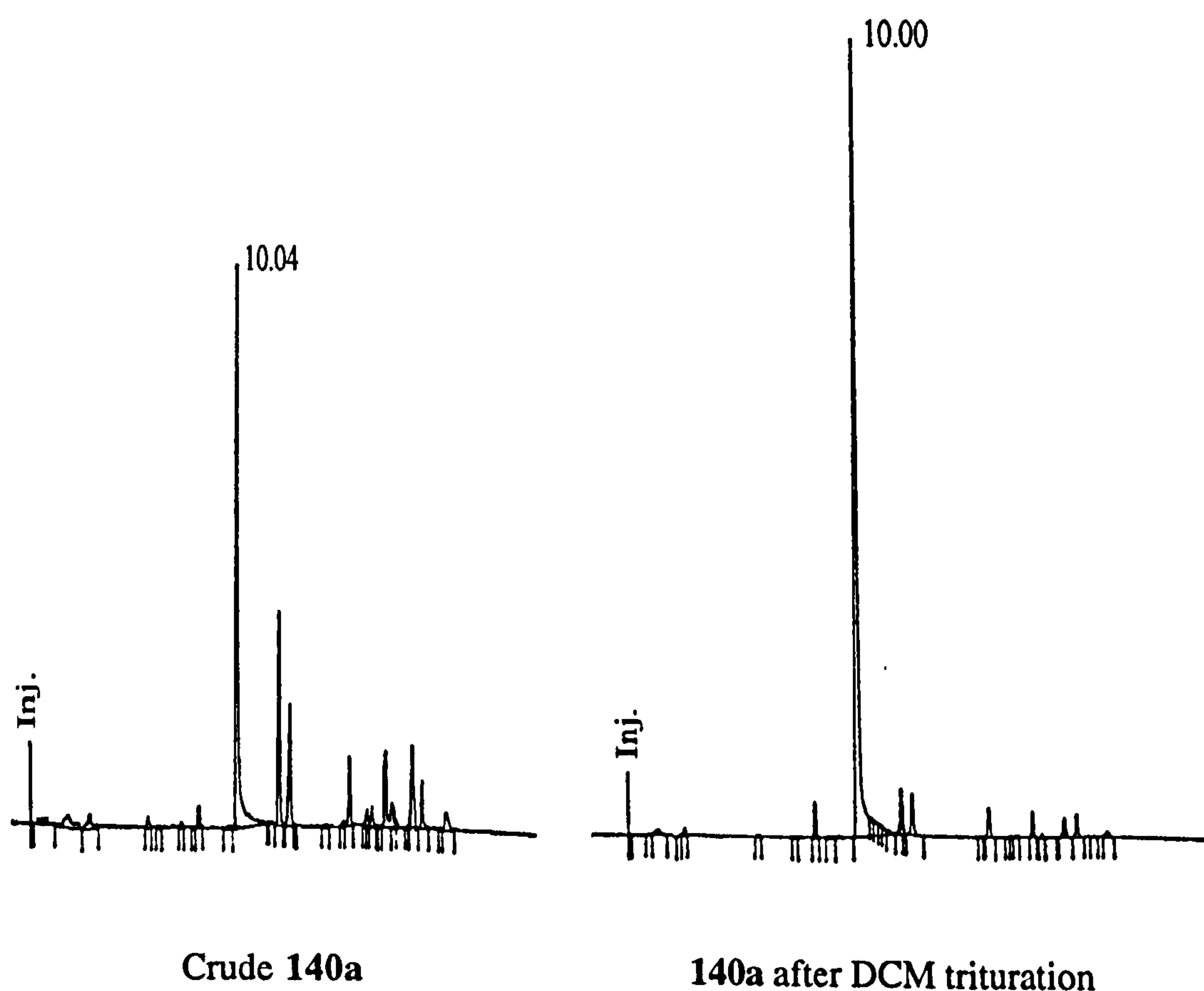
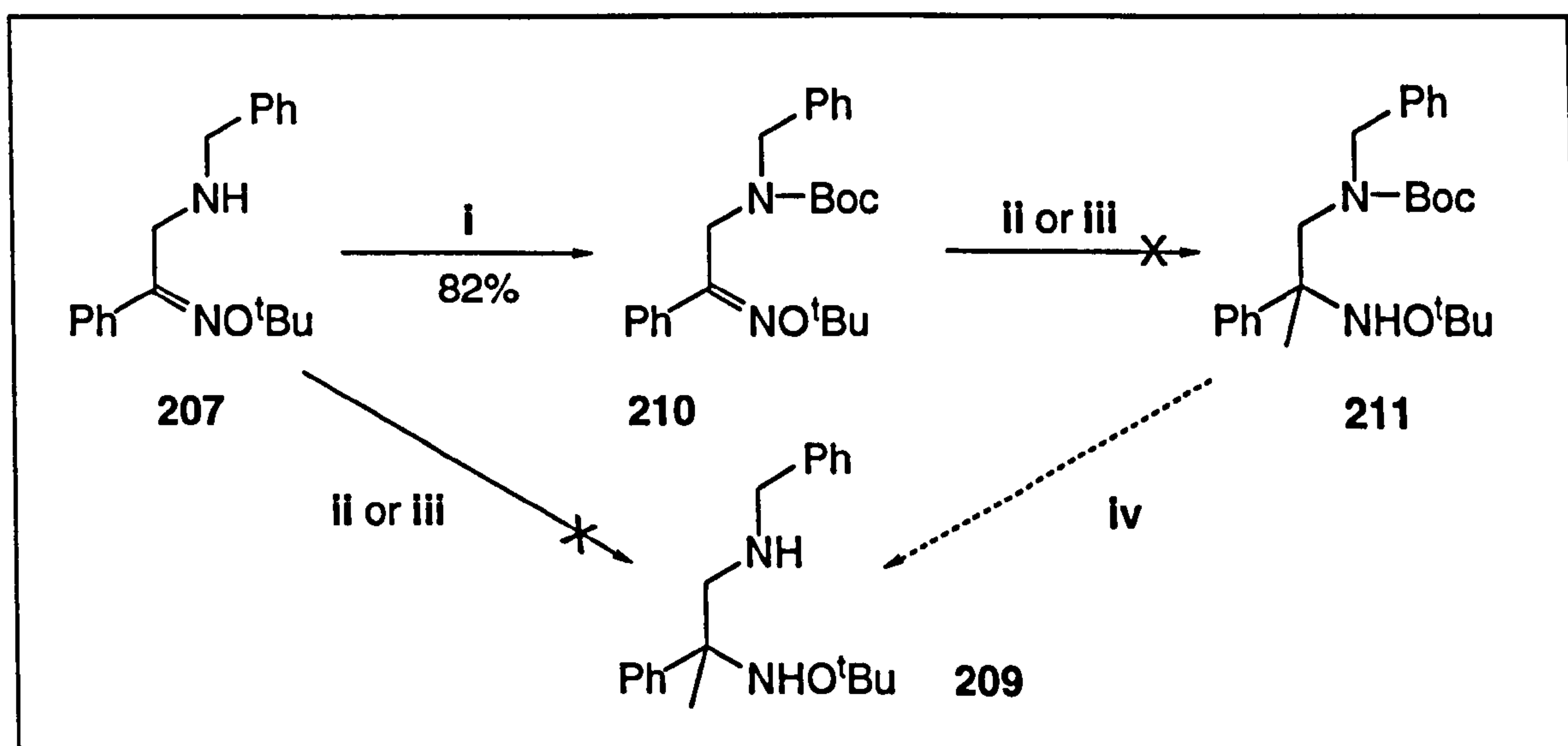


Figure 21 : HPLC analysis of dihydrochloride salt **140a** before and after DCM trituration.

We had initially attempted unsuccessfully to reduce the *O-tert*-butyl oxime **207** with sodium cyanoborohydride, and this prompted us to consider attack on this oxime with an organometallic reagent. Thus, we hoped to prepare hydroxylamine **209** using methyllithium

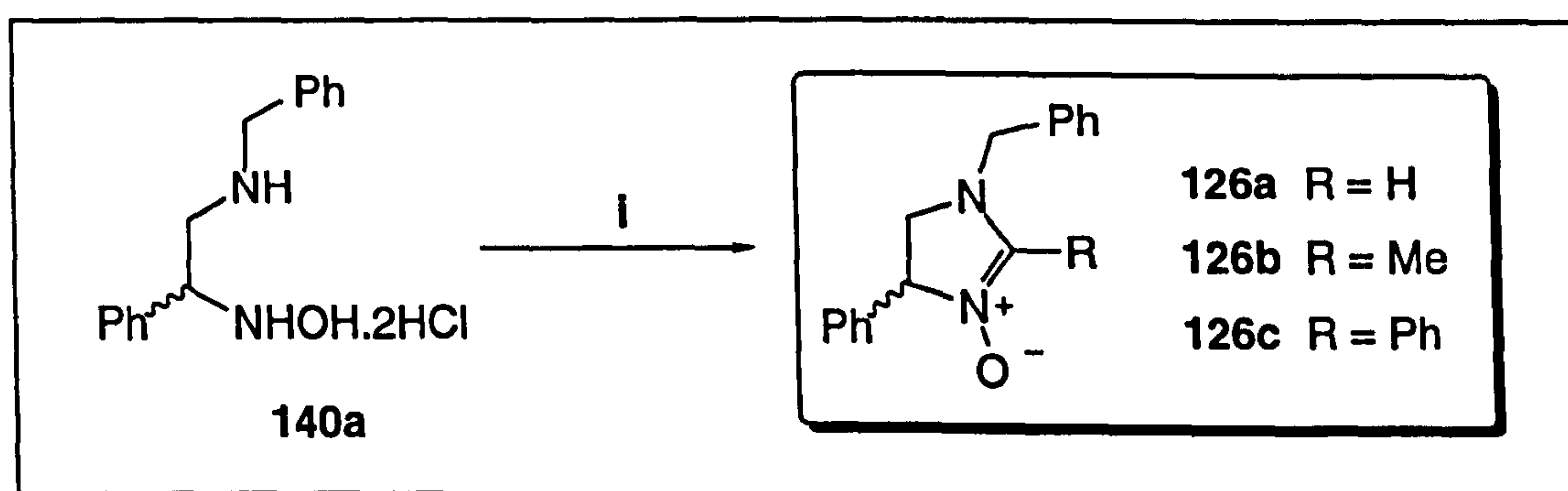
at -75°C , but we were to enjoy no success, even when the oxime was treated with a Lewis acid ($\text{BF}_3\cdot\text{Et}_2\text{O}$) prior to addition of the alkyllithium (Scheme 72). Protection of the benzylamino function as the *tert*-butoxycarbamate in a hope to discourage unwanted side reactions, proceeded in high yield to afford **210** as a mixture of carbamate rotamers and oxime geometric isomers. ^1H NMR analysis of **210** in a mixture of CDCl_3 and $\text{d}_6\text{-DMSO}$ showed collapse of the rotamer signals at 50°C , to become sharp singlets by 110°C and allow characterisation of both oxime isomers. Attempted alkylation of **210** with methyl lithium at -75°C afforded none of the desired hydroxylamine **211** after warming to 20°C overnight. When the experiment was repeated with initial treatment with $\text{BF}_3\cdot\text{Et}_2\text{O}$, only 6% of **210** was returned, along with 47% of the deprotected oxime **207**. Fortunately, our successful reduction of **207** with $\text{BH}_3\cdot\text{THF}$ made our problems here academic.



Reagents : i, Boc_2O , Et_3N , DCM, 20°C , 1.5h; ii, MeLi, Et_2O , -75°C , 18h; iii, $\text{BF}_3\cdot\text{Et}_2\text{O}$, Et_2O , -75°C , then ii; iv, *Proposed reagents* : 2M aq. HCl.

Scheme 72

The free hydroxylamino amine **140** was unsuccessfully subjected to the cyclisation conditions developed for the synthesis of the 1-benzyl-4-phenyl-2-imidazolines **128**, under reflux with triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid. Similarly, these conditions did not convert the *O*-*tert*-butylhydroxylamino amine **208** into the desired nitron **126a**; we had speculated that the acidic conditions might promote deprotection as well as heterocycle formation. When a slurry of the dihydrochloride salt **140a** in DCM was treated with triethyl orthoformate and warmed to reflux we were able to observe consumption of the solid within 1 hour, and removal of the solvent afforded the 3-benzyl-5-phenyl-2-imidazoline-1-oxide **126a** or '2-H nitron' in quantitative yield (Scheme 73). Similarly, the '2-methyl nitron' **126b** was prepared using triethyl orthoacetate in a quantitative yield and the '2-phenyl nitron' **126c** was detected by mass spectrometry in a mixture prepared in this way from triethyl orthobenzoate.



Reagents : i, RC(OEt)₃, DCM, Δ, 1h.

Scheme 73

In work beyond the scope of this report, it is clear that the potential exists in our synthesis to prepare these nitron reagents in enantiopure form. Firstly, we might introduce enantiopurity by reduction of the *O*-*tert*-butyl oxime **207** with asymmetric induction, to afford the homochiral hydroxylamine (*R*)- or (*S*)-**208**. Asymmetric oxime reduction has

been achieved using a number of systems^{260,261} including chiral oxazaborolidine complexes prepared from homochiral aminoalcohols and borane-complexes.²⁶²⁻²⁶⁷ The stereochemistry of the isolated hydroxylamine is known to depend on the stereochemistry of the complex as well as the geometry of the oxime (that is to say *E*- and *Z*-oxime isomers give rise to different stereochemistry in the isolated hydroxylamine). Secondly, the *O*-*tert*-butylhydroxylamino amine **208** or the dealkylated hydroxylamine **140** might be resolved by fractional crystallisation^{268,269} of the diastereomeric salts formed by treatment with a homochiral carboxylic acid. It might then be possible to assign the absolute stereochemistry of our reagents by X-ray crystallographic analysis of the salts formed with a homochiral carboxylic acid.

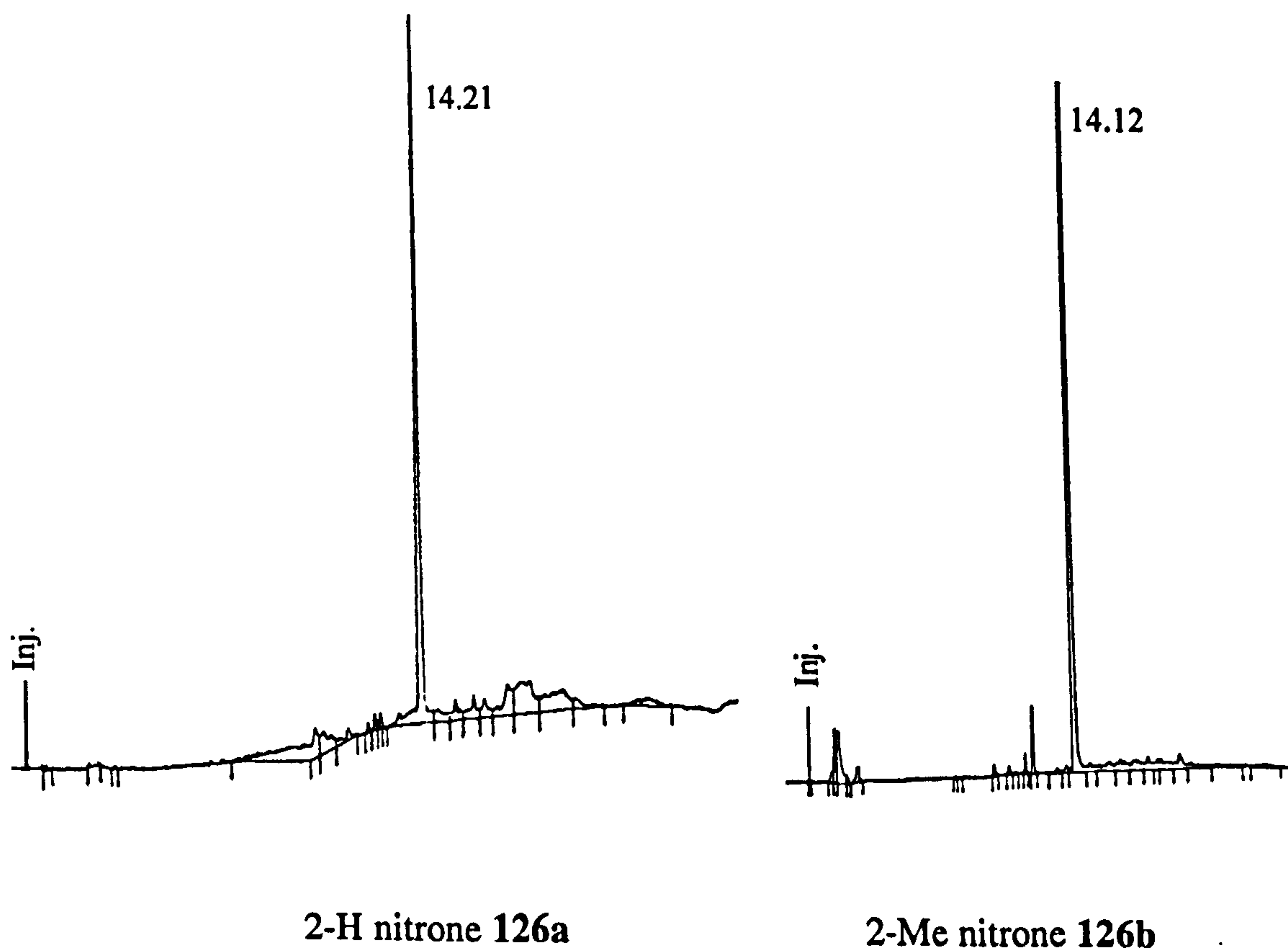


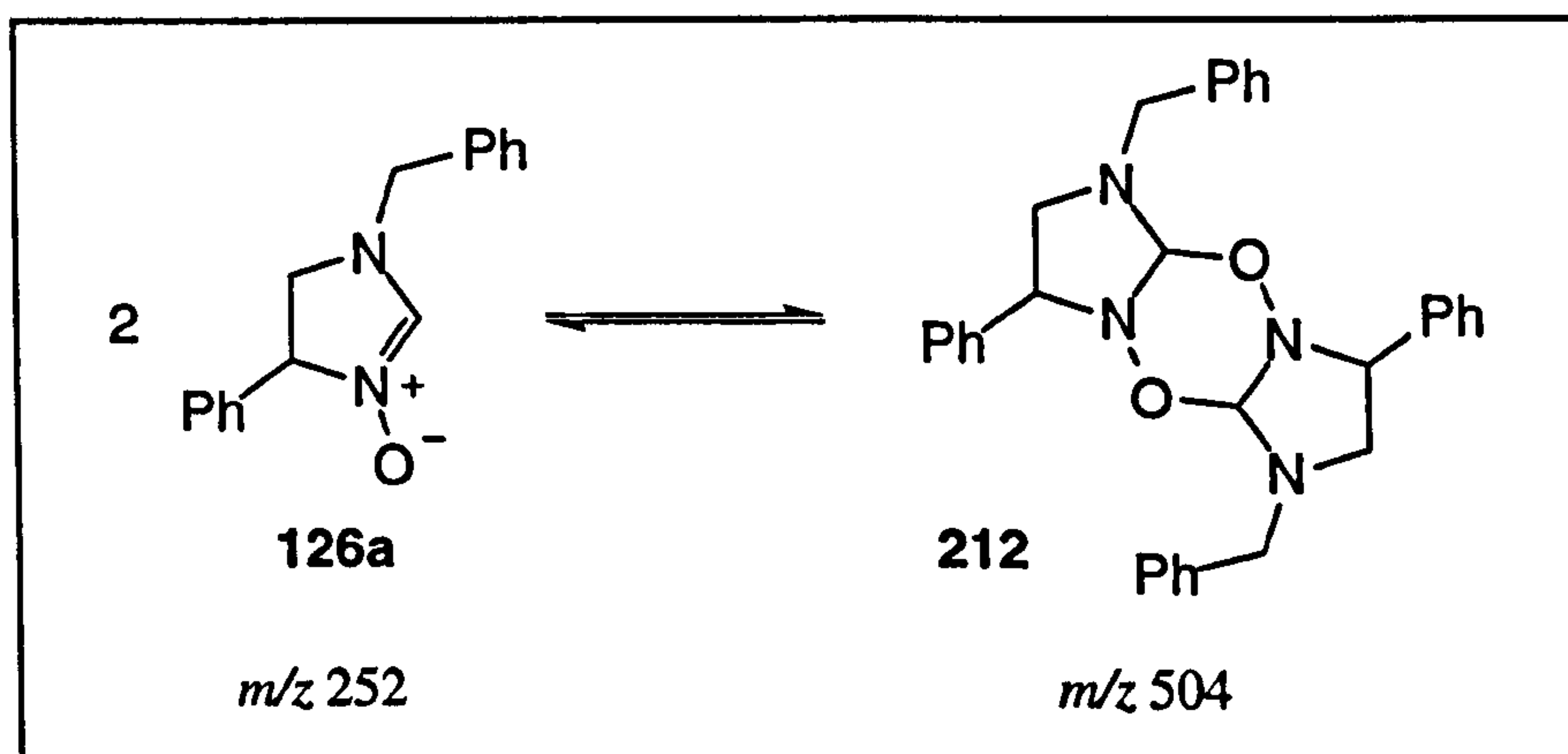
Figure 22 : Reverse-phase HPLC traces of 2-imidazoline nitrones **126a and **126b**.**

Our synthesis of these 2-imidazoline nitrones was carried out in the presence of 2 equivalents of HCl liberated from the dihydrochloride salt **140a**, and so the nitrones we isolated will presumably be present as the hydrochloride. Therefore, it was not feasible to monitor the reaction using conventional silica TLC, and so they were analysed by the reverse-phase HPLC method developed earlier to observe the formation of **140a** from **208** (Appendix II). This system allowed us to follow the reaction using one drop of the crude reaction mixture, which was diluted to 4ml with solution A and up to 20 μ l loaded into the injection loop of the HPLC instrument. Thus, we distinguished the salt **140a**, eluted at approximately 10.0 minutes, from the salt of the 2-H nitrone **126a** with a retention time of approximately 14.2 minutes or the salt of the 2-methyl nitrone **126b** eluted at 14.1 minutes (Figure 22). We, therefore, were easily able to determine whether the hydroxylamino amine had been consumed and in this way we found the nitrone **126a** to be the only product after warming to 60°C for 1 hour with triethyl orthoformate.

Coates and Ashburn have reported the synthesis of 2-substituted oxazoline nitrones using amide acetals.¹⁰⁰ Using their method we detected the presence of the 2-H nitrone **126a** by atmospheric pressure chemical ionisation mass spectrometry (positive ion mode), or APCI⁺, after stirring a slurry of **140a** with dimethylformamide diethylacetal in dry DCM for 18 hours. Here we observed m/z 253 (MH⁺) with intensity of 8% as well as 237 (MH⁺-O) at 100% intensity. Subsequent HPLC analysis showed this solution to be a mixture of the nitrone **126a** and the salt **140a** (4.7:1), thus proving this method less effective than our orthoester methodology.

These nitrones were sufficiently stable to be characterised by NMR in CDCl₃ and by APCI⁺ mass spectrometry (from methanol solution). The APCI⁺ mass spectrum of the 2-H nitrone **126a** showed the protonated molecular ion (MH⁺) at m/z 253 (15% intensity) as well

as the deoxygenation fragment 238 (MH^+-O), characteristic of nitrones and N-oxides, as the base peak. We observed a peak at 505 (4%) equivalent in mass to 2 molecules of **126a**, and tentatively concluded that under these conditions this nitron forms a dimer such as **212** (m/z 504) (Scheme 74).

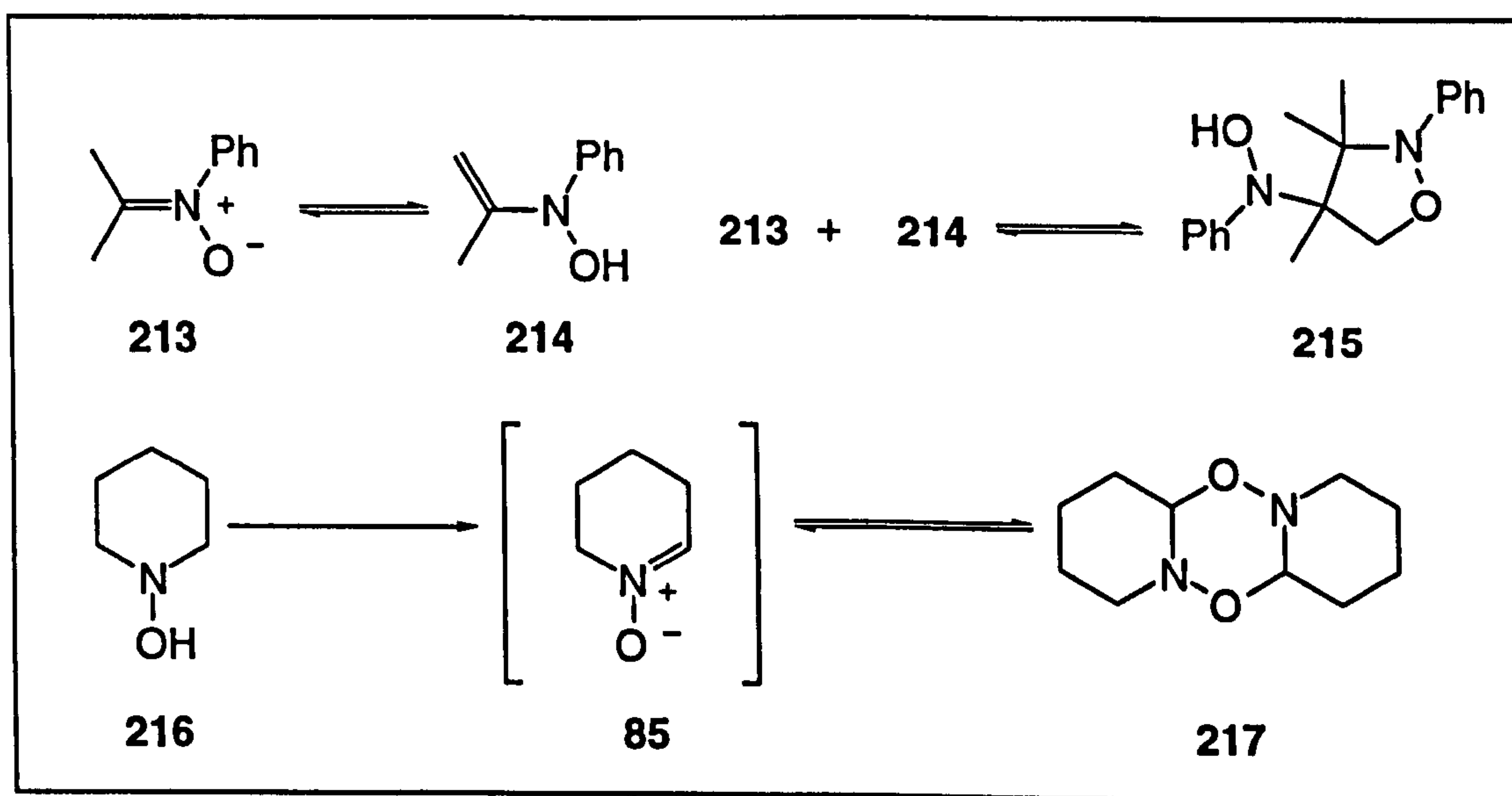


Scheme 74

Our proposal is supported by many well-documented cases of nitron dimer- and trimerisation from the literature. Certain acyclic nitrones have been shown to form self-condensation products. For example, C-dimethyl-N-phenyl nitron **213** reacts with the α,β -unsaturated hydroxylamine **214** with which it is in equilibrium, to afford the 4-hydroxylaminoisoxazolidine cycloadduct **215** (Scheme 75).²⁷⁰⁻²⁷⁷ However, the nitron **126a** cannot tautomerise in this way, and so we discount this type of product. By contrast, some cyclic nitrones can give rise to the 'head-to-tail' dimer. Here, the 'head-to-tail' description is used to indicate that the atoms of the new ring are arranged in the order N-O-C-N-O-C in the dimeric species, rather than the 'head-to-head' dimer where they are arranged N-O-C-C-O-N. An example is the oxidation of N-hydropiperidine **216** which affords the tricyclic dimer **217** on attempted isolation, rather than the desired 1,2-dehydropiperidine-N-oxide **85**.²⁷⁸ The monomeric nitron **85** can be made available for

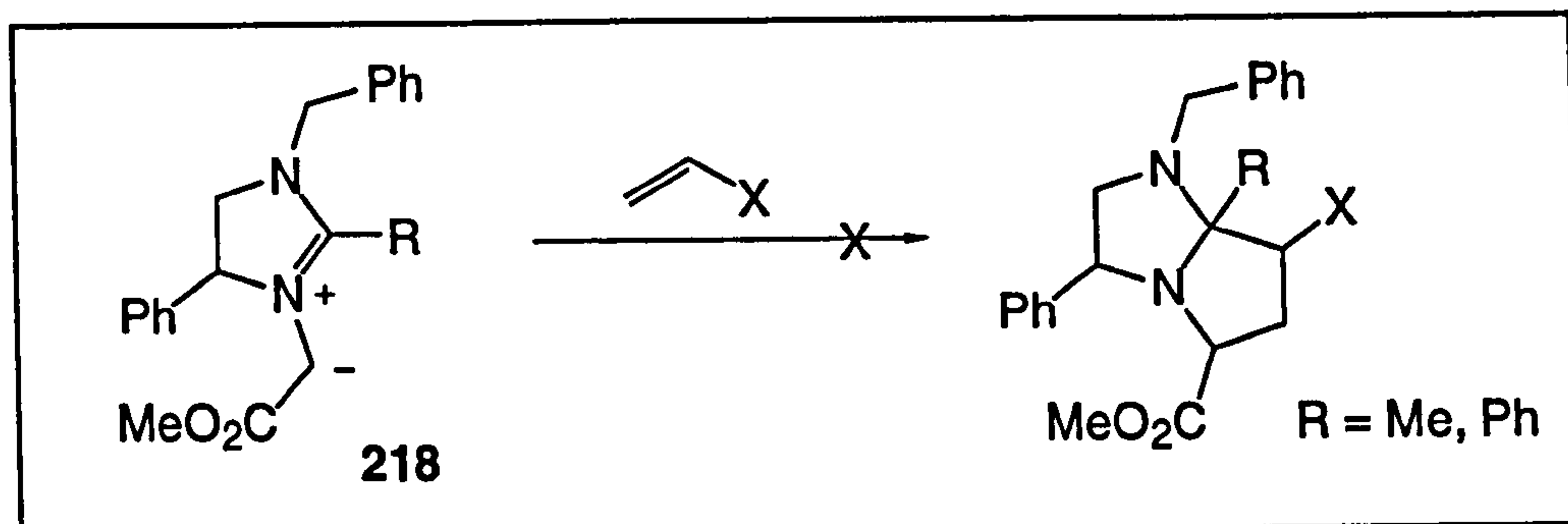
1,3-dipolar cycloaddition chemistry by thermal cracking of the dimer **217**. Preferably, oxidation to the nitron **85** is carried out in solution with an alkene dipolarophile for *in situ* trapping of the nitron once formed.

Other evidence to support a proposed dimer structure such as **212** (m/z 504) is provided by the peaks at m/z 489 (7%) and 473 (10%) corresponding to partial and complete deoxygenation of the dimer with loss of one and two O atoms respectively, *via* rearrangement to an unknown structure. In the APCI⁺ mass spectra of the 2-methyl and 2-phenyl nitrones, the protonated molecular ion (MH⁺) is observed and the base peak corresponds to nitron deoxygenation, but with no suggestion of dimerisation. We propose that this may be due to the steric hindrance offered by a carbon substituent at the 2-position of the nitron blocking one of the reacting centres in dimer formation.



Scheme 75

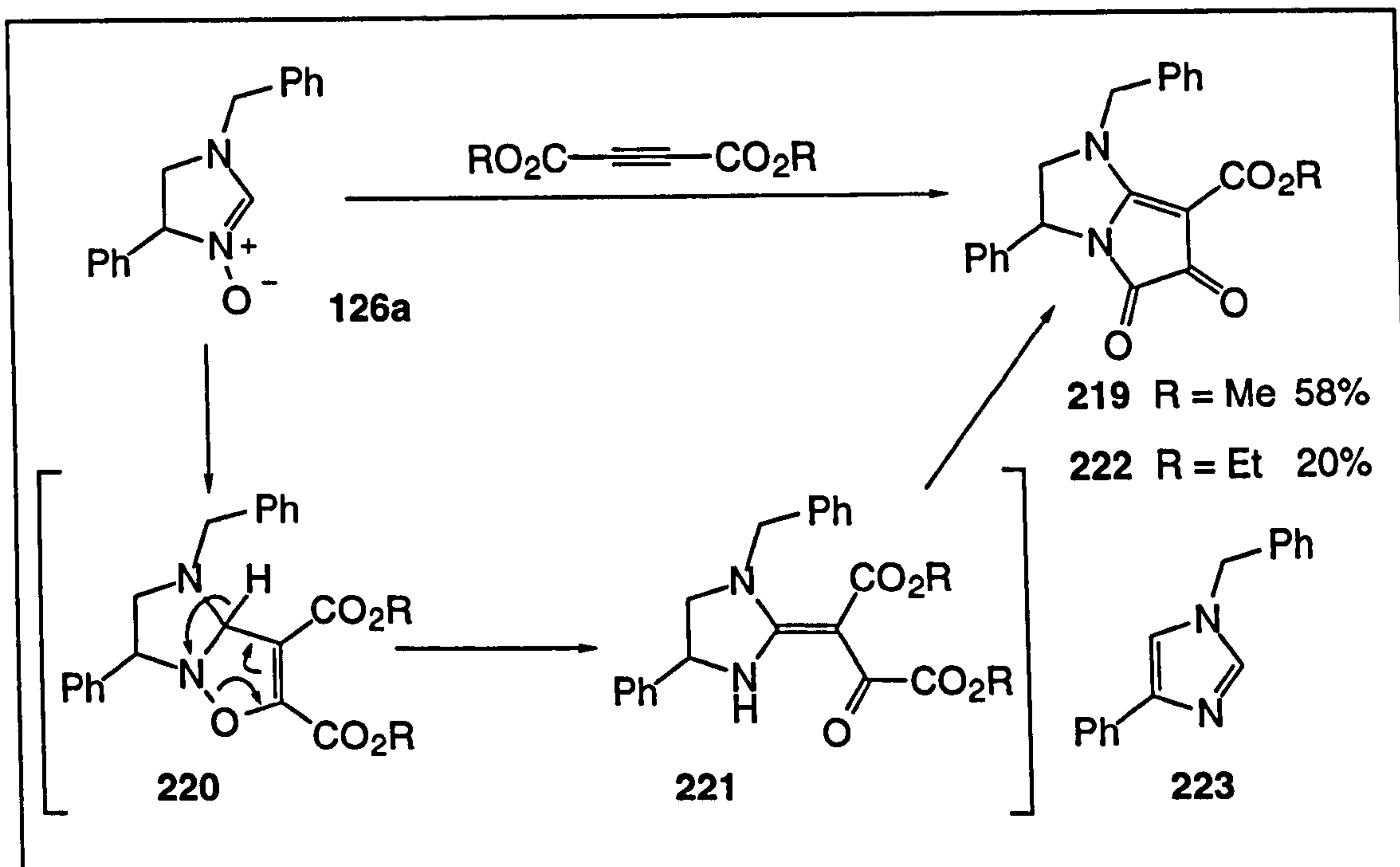
2.3 1,3-Dipolar cycloaddition reactions.



Scheme 76

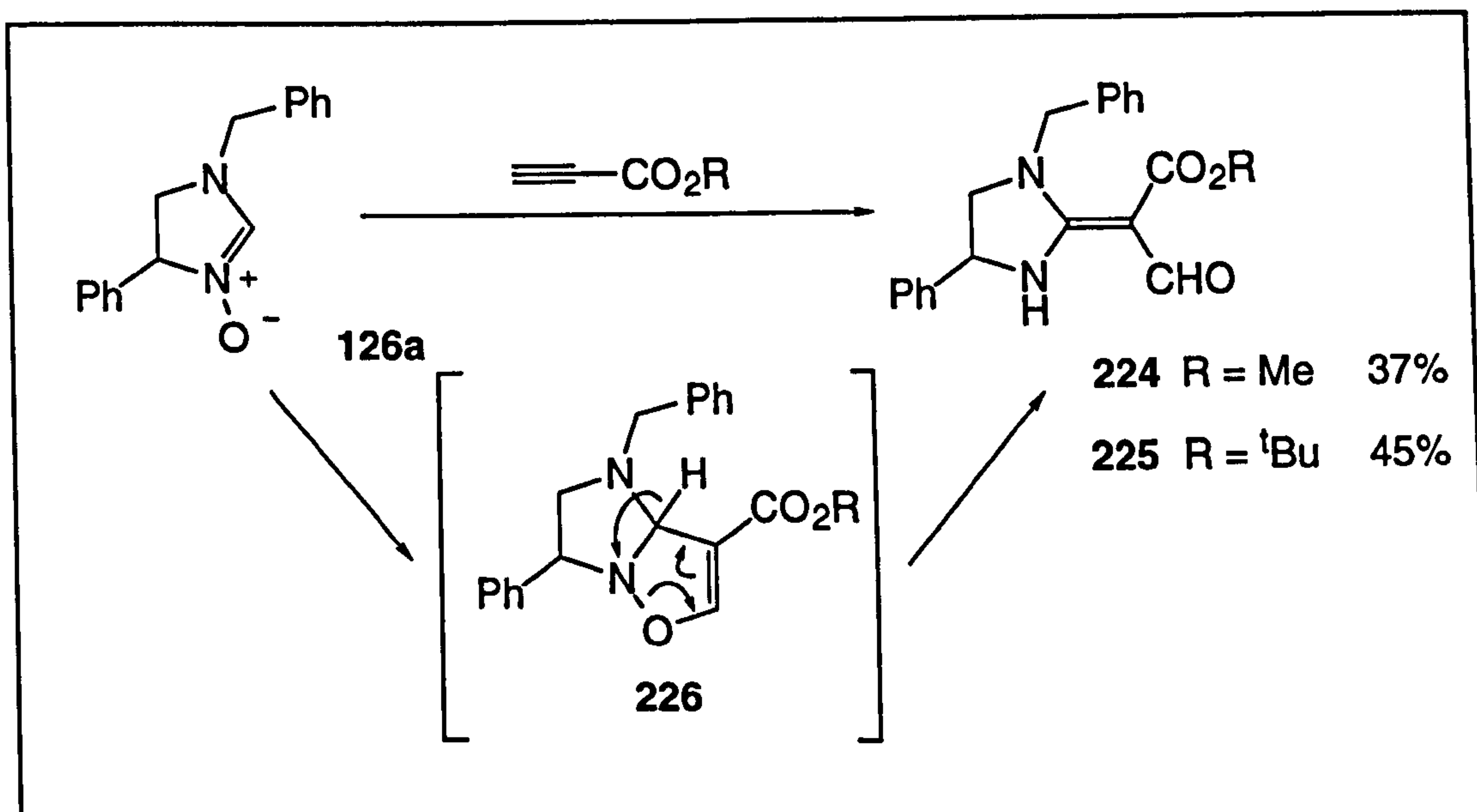
Our choice of nitron to take forward into dipolar cycloadditions was affected by the experience of previous workers in our group who had found that no 1,3-dipolar cycloaddition took place with the C-2 substituted 2-imidazoline azomethine ylides **218** ($R \neq H$) (Scheme 76).

We therefore chose the least substituted 2-H nitron **126a**, and took dimethyl acetylenedicarboxylate (DMAD) as our initial dipolarophile on the basis of its normally high cycloaddition reactivity. Our studies thus far had shown that whilst these nitrones could be prepared in essentially quantitative yield, the isolated material may suffer decomposition. It was therefore decided that a one-pot procedure combining *in situ* generation of the nitron dipole followed by immediate addition of the dipolarophile would be most prudent. Our nitron was prepared as described in Section 2.2.3, before addition of 2 equivalents of the hindered base N,N-diisopropylethylamine (Hünig's base) at 40°C, to neutralise the HCl generated from the dihydrochloride salt **140a**, followed by 1.25 equivalents of DMAD. This mixture was stirred at 40°C for 18 hours then treated with saturated aqueous NaHCO₃ and extracted into DCM. Drying and removal of the solvent gave an oily residue which was purified by column chromatography to afford the keto lactam **219** (37%) rather than the desired cycloadduct **220** (Scheme 77).



Scheme 77

We propose that **219** is produced from a rearrangement reaction of the cycloadduct **220**, initiated by a 1,5-shift (C-to-N) of the bridgehead proton and N–O bond lysis, to afford the α,β -unsaturated ketodiester **221**. Spontaneous ring-closure by lactamisation onto the free benzylamino function affords the isolated keto lactam **219**. The product of this reaction was unaffected by changing the base to Et_3N , although the yield was improved to 58%; diethyl acetylenedicarboxylate gave the analogous cycloadduct **222** (20%) along with the formal product of dehydration of nitrone **126a**, the imidazole **223**. We resolved to probe the generality of this reaction using mono-carboxylates of acetylene. Thus, we treated the nitrone **126a** separately with methyl and *tert*-butyl propiolate to afford the α,β -unsaturated keto aldehydes **224** (37%) and **225** (45%), respectively. Their formation can be easily rationalised *via* our proposed 1,5-H shift mechanism from the primary cycloadducts **226** (Scheme 78). Nitrone **126a** was then reacted with phenyl isocyanate (PhNCO), another highly reactive dipolarophile, but no cycloadduct could be isolated from a complex mixture of products.

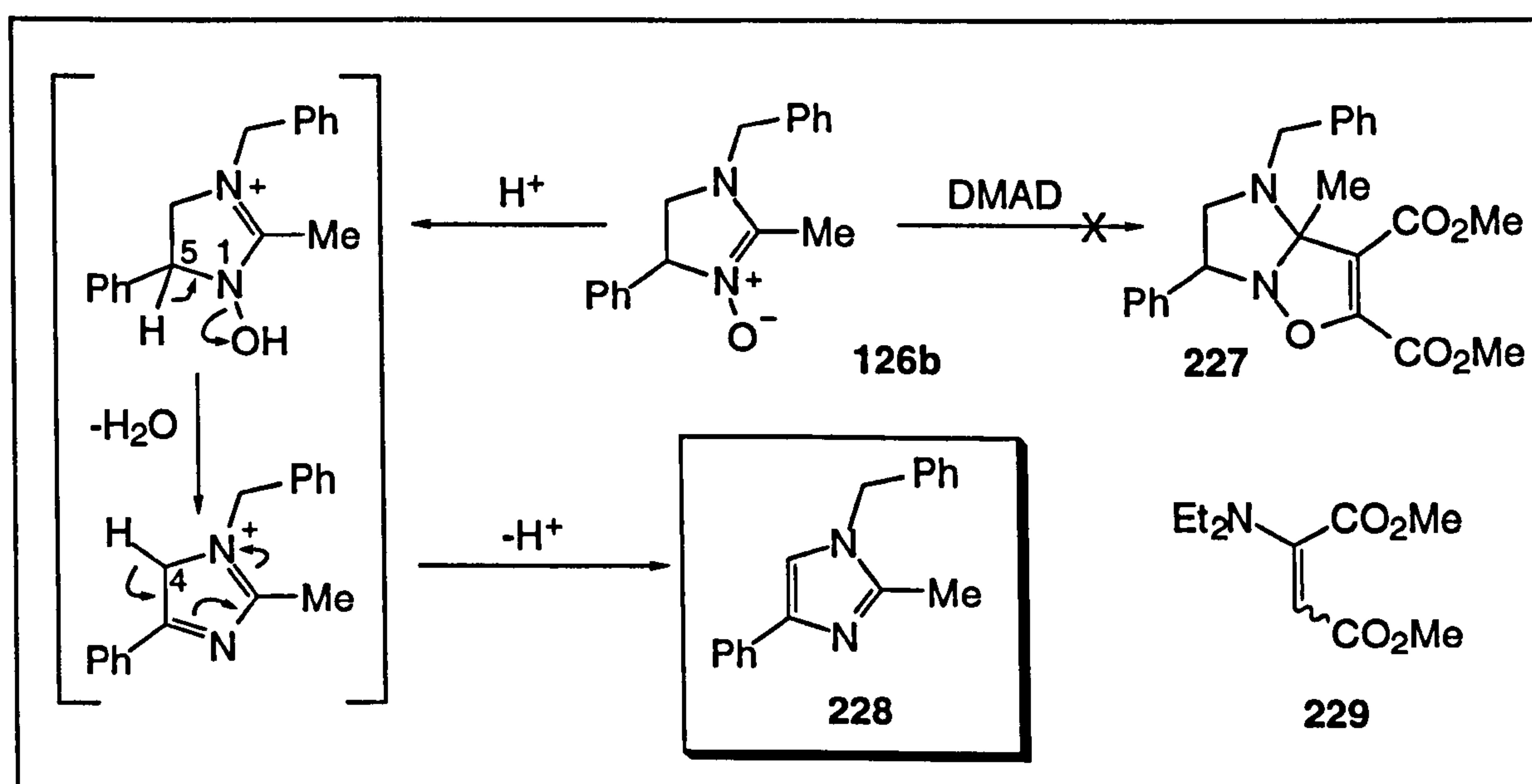


Scheme 78

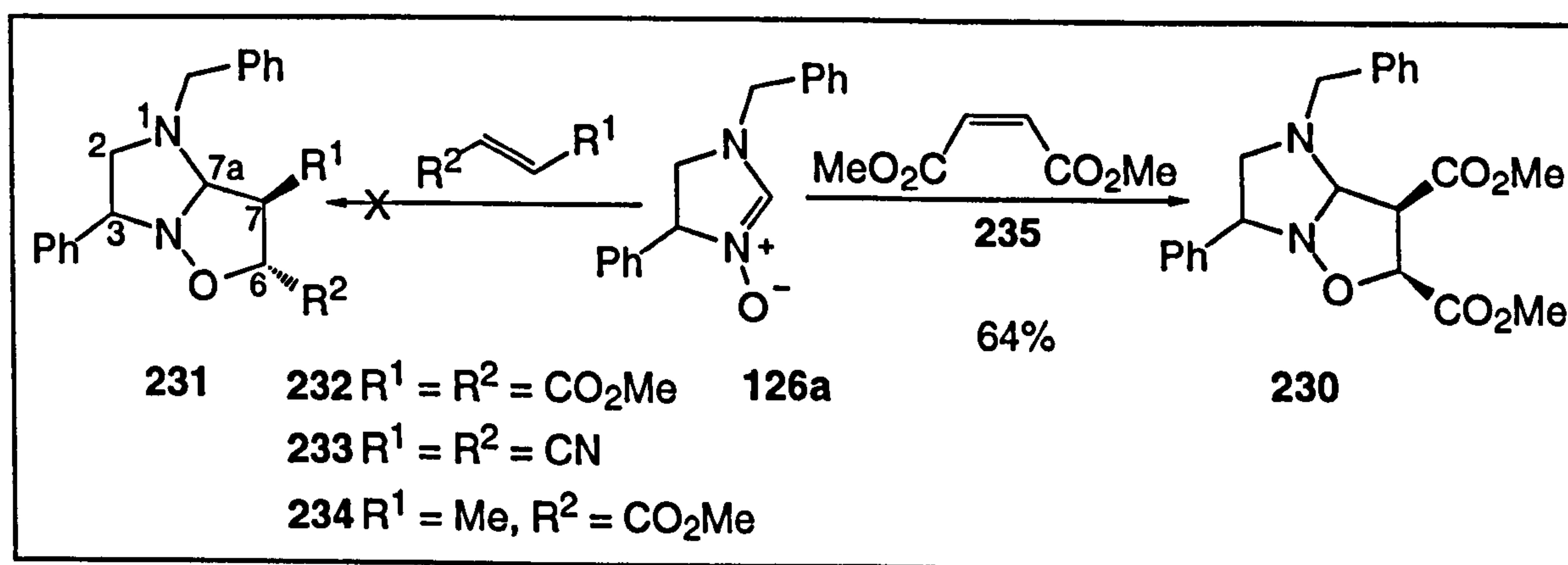
Encouraged by our first cycloadditions with these nitrones we sought to discourage the rearrangement reaction by the use of the 2-methyl nitrone **126b** which would give cycloadducts having no bridgehead proton to participate in the 1,5-shift. Thus, the nitrone was prepared by treatment of a solution of salt **140a** in dry DCM with 1.25 equivalents of triethyl orthoacetate and heating for 1 hour at reflux under a nitrogen atmosphere, before addition of 1.25 equivalents of triethylamine and the dipolarophile. Reaction of **126b** with DMAD did not afford the desired cycloadduct **227** (Scheme 79) nor any product from rearrangement of **227**. Similarly, no cycloadducts or rearrangement products were isolated from the reaction of this nitrone with PhNCO , methyl propiolate, dimethyl maleate, methyl acrylate or maleic anhydride. As we had seen in the reactions of **126a**, we were often able to isolate the formal 'dehydration product' 1-benzyl-2-methyl-4-phenyl-1*H*-imidazole **228**. We propose that the first step in the formation of **228** is the protonation of the N-oxide **126b** to set up loss of water across the N-1 to C-5 bond. The loss of the C-4 proton is then driven by aromatisation of the ring and makes this process catalytic in H^+ . We tried to recreate this reaction by prolonged reflux of this nitrone in toluene with the drying agent P_2O_5 but without

success. We propose that the analogous imidazoline **223** is also formed by this mechanism.

In the case of DMAD as the dipolarophile, the diester **229** was identified which is a known condensation product of this acetylene reagent with triethylamine *via* the elimination of ethene (Scheme 79).²⁷⁹⁻²⁸¹



Scheme 79



Scheme 80

We concluded that C-2 functionalisation was not tolerated in these nitrones, even with the most reactive dipolarophiles. We, therefore, refocussed our attention on the 2-H

nitron **126a** and resolved to conduct a series of cycloaddition reactions with alkene dipolarophiles which (if our mechanistic proposal is valid) should disfavour the rearrangement described above for alkyne dipolarophiles. Our study commenced with symmetrical alkenes in order to restrict the potential product mixture by eliminating the possibility of generating mixtures of regioisomers. The 2-H nitron **126a** was prepared in toluene solution before addition of 1.25 equivalents of Et₃N and 1.25 equivalents of *trans* alkene dipolarophile (Scheme 80) and heating overnight at 60°C.

Huisgen has shown that the geometry of substituents in the alkene dipolarophile is always retained in the cycloadduct of a 1,3-dipolar cycloaddition reaction.³² Therefore, the relative stereochemistry of the cycloaddition products from the *E*- and *Z*-isomers of a chosen alkene with a given nitron should differ only in the geometry at the former alkene stereocentres. This is reflected in Scheme 80, where the stereochemistry at C-6 and C-7 of the imidazoisoxazole cycloadducts has been arbitrarily assigned to distinguish between the expected cycloadduct from reaction of a *cis* alkene **230** from that of a *trans* alkene **231**. However, no reaction was observed with the *trans* alkenes dimethyl fumarate **232**, fumaronitrile **233** or methyl crotonate **234**. This suggests that the dipole **126a** does not tolerate any *endo* component to the transition state, which must exist for the reaction of these *trans* alkenes. We proceeded to react the 2-H nitron **126a** with *cis* alkenes under the same conditions, starting with dimethyl maleate **235**. After stirring a toluene solution of **126a** with 1.25 equivalents of DMM at 60°C for 18 hours we were delighted to isolate the cycloadduct **230** as a colourless oil after chromatography (64%).

The partial stereochemistry in Scheme 80 is assumed; in order to determine the relative stereochemistry of this material, it was examined by difference nuclear Overhauser enhancement spectroscopy (nOe) (Figure 23). This NMR technique exploits the ability of

protons to interact not only through bonds but also through space with other proximal protons. In the nOe experiment, the normal ^1H spectrum is acquired but with simultaneous irradiation at a frequency corresponding to a chosen proton signal in the spectrum. An increase in the intensity of any other proton resonance in the spectrum indicates that the irradiated and enhanced protons are sufficiently close to interact through space. The difference nOe spectra are obtained by subtraction of the normal ^1H spectrum from the enhanced spectra. It is important to note that the lack of enhancement between chosen protons does not prove that they are non-adjacent, but may merely indicate the presence of other relaxation mechanisms.

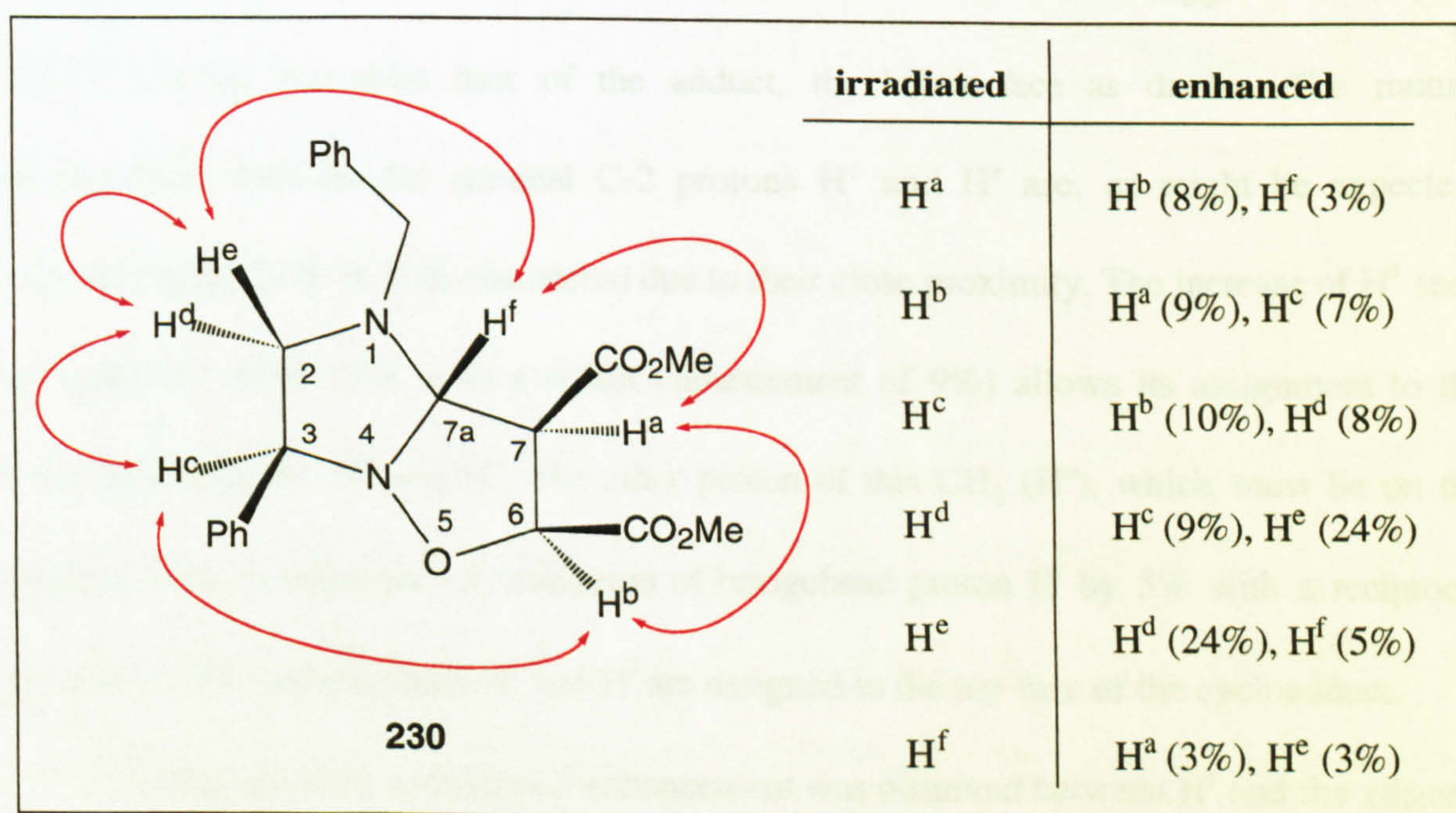


Figure 23 : Nuclear Overhauser enhancements for cycloadduct **230**.

Using this technique, not only can adjacent protons be identified, but the strength of the interaction can be quantified by the increase of the integrated peak area of the affected protons. For ^1H spectra, an enhancement of +1% is considered significant, but values may be far greater. It has been shown that the enhancements decrease by a factor of r^6 where r is

the distance between the interacting nuclei²⁸² and are generally observed between protons separated by up to 4Å. The chiral racemic hydroxylamino amine **140** we had prepared would ultimately lead us to chiral racemic nitrones. Therefore, we would isolate chiral racemic cycloadducts but the nOe technique would still allow us to characterise the relative stereochemistry *via* these enhancements of our products (arrowed in Figure 23) and so map the profile of the 2-H nitrone in its 1,3-dipolar cycloaddition chemistry.

Irradiation of the α -proton of the C-7 ester, H^a, of cycloadduct **230** produced an enhancement of the signal of the α -proton of the adjacent C-6 ester, H^b, by 8%. A reciprocal enhancement of H^a by 9% was observed by irradiation of H^b; irradiation of H^b also augments the signal of H^c at C-3 by 7% with a return enhancement of 10%. This suggests that H^a, H^b and H^c occupy the same face of the adduct, the lower face as drawn. The mutual enhancements between the geminal C-2 protons H^d and H^e are, as might be expected, relatively large (24% in both directions) due to their close proximity. The increase of H^d seen on irradiation of H^e (8%, with a return enhancement of 9%) allows its assignment to the lower face with H^a, H^b and H^c. The other proton of this CH₂ (H^e), which must lie on the opposite face, is enhanced on irradiation of bridgehead proton H^f by 5% with a reciprocal increase of 3%, and thus both H^e and H^f are assigned to the top face of the cycloadduct.

To our surprise, a reciprocal enhancement was observed between H^f and the adjacent proton H^a (with zero scalar coupling in the ¹H NMR spectrum), which we had thus far assigned to opposite faces of the cycloadduct. A simple molecular model of cycloadduct **230** shows that H^f and H^a can adopt a dihedral angle of approximately 90° through ring-flip of the bicyclic skeleton but only if these protons have a *trans* arrangement. Therefore, from the theoretical dependence of the ¹H NMR coupling constant on dihedral angle given by the Karplus relation, a 90° dihedral angle should give rise to near-zero scalar coupling between

these adjacent protons.²⁸³ A similar bicyclic isoxazolidine system **236** has been synthesised by Ali *et al.* (Figure 24). The H^x proton appears as a doublet in the ¹H spectrum, which the authors claim is indicative of coupling between H^x and H^z only. Thus, there is zero scalar coupling between H^x and H^y suggesting a dihedral angle of H^x–C–C–H^y of approximately 90°.284

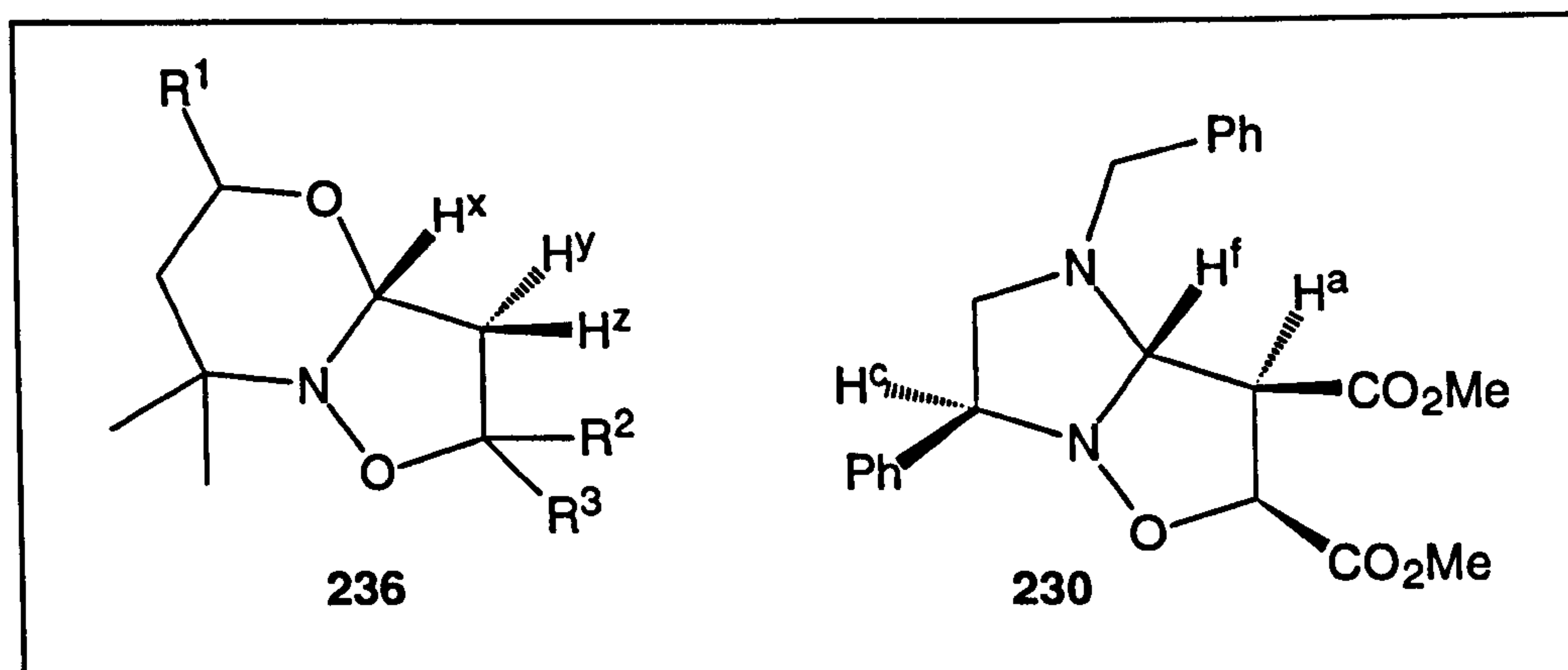


Figure 24

We were then able to crystallise the cycloadduct **230** from methanol and obtained an X-ray crystal structure which confirmed our nOe assignments (Figure 25). In the crystalline state, the dihedral angle between H^f and H^a was measured at 92.1°, corroborating our findings. Our quantitative difference nOe experiment was later repeated using the more sophisticated, qualitative, 2-dimensional "NOESY" technique, which was found to agree with our interpretation.

The assignment of relative stereochemistry allows us to make several conclusions about the transition state of the 1,3-dipolar cycloaddition reaction of the nitron **126a** with DMM. The *cis* relationship between the two ester α-protons (H^a and H^b) is maintained as was expected - the alkene geometry is always maintained during the concerted bond-forming process of the cycloaddition.³² The stereochemistry at the C-6 and C-7 stereocentres is

evidence of the preference for the *exo* transition state. It is clear that only *exo* approach would lead to the observed adduct **230**, with the *endo* transition state producing the diastereomer **237** (Scheme 81). Most importantly, the *trans* relationship between H^c and H^f indicates the complete diastereofacial selectivity of this 2-imidazoline nitrone reagent. It is the steric bulk of the phenyl group adjacent to the nitrone nitrogen atom that directs incoming dipolarophiles to the less hindered face. The bridgehead C-7a proton (H^f) and the C-3 phenyl group will thus share the same face of the nitrone in the favoured transition state, and so the isolated product **230** reflects this geometry.

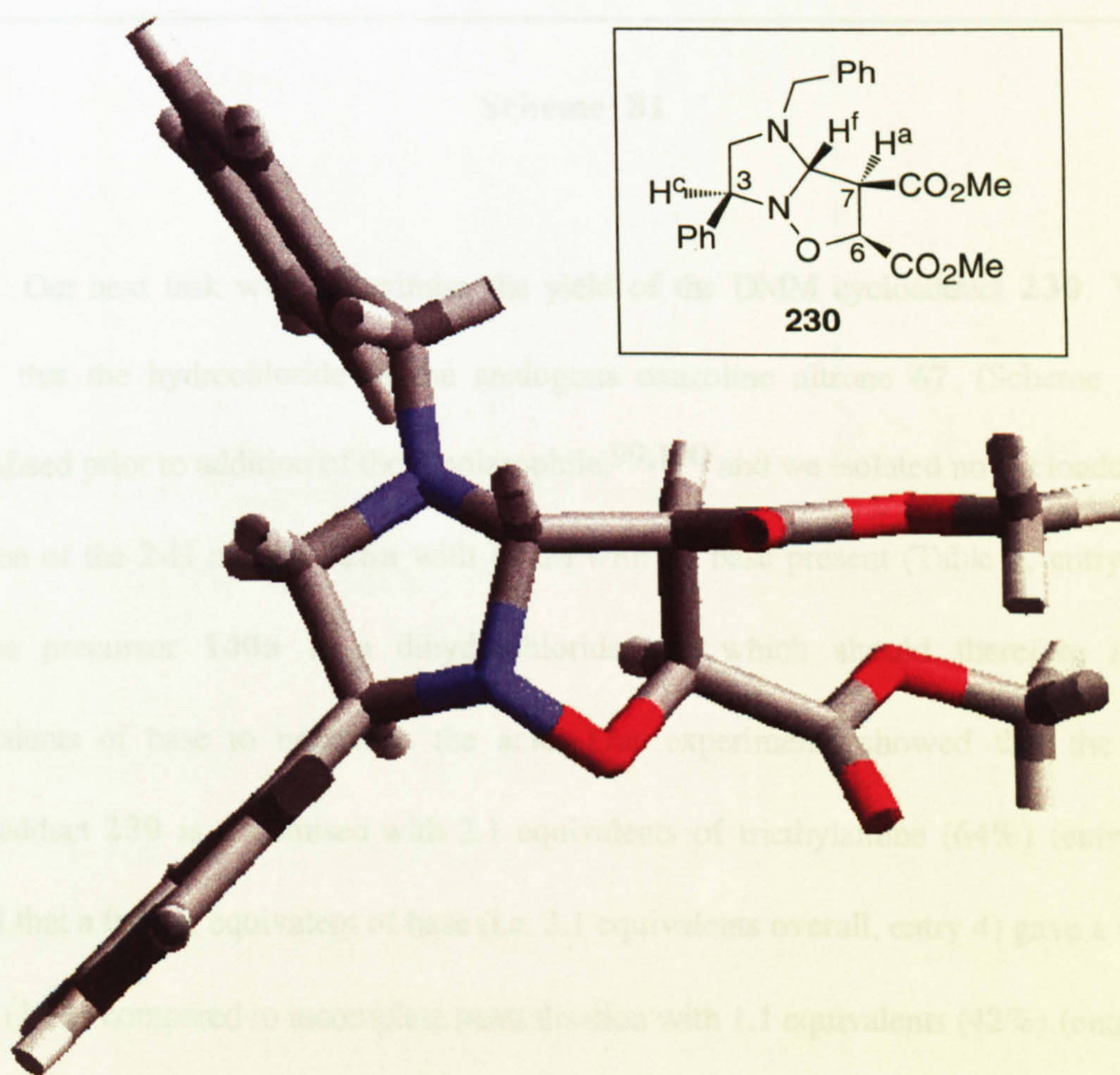
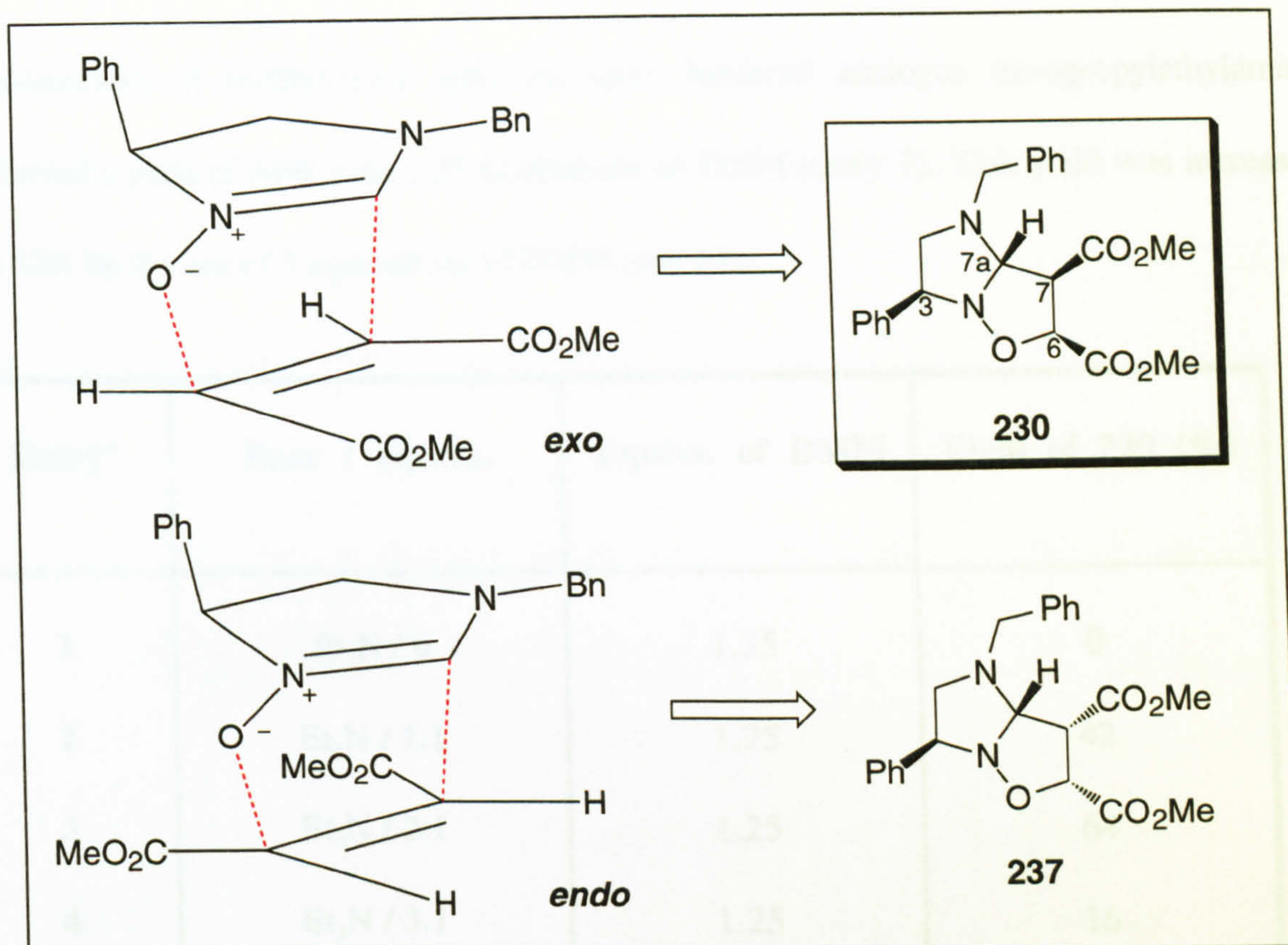


Figure 25 : X-ray crystal structure of cycloadduct **230**.



Scheme 81

Our next task was to optimise the yield of the DMM cycloadduct **230**. We were aware that the hydrochloride of the analogous oxazoline nitronium **67** (Scheme 28) was neutralised prior to addition of the dipolarophile,^{99,100} and we isolated no cycloadduct from reaction of the 2-H nitronium **126a** with DMM with no base present (Table 3, entry 1). The nitronium precursor **140a** is a dihydrochloride salt which should therefore require 2 equivalents of base to neutralise the acid. Our experiments showed that the yield of cycloadduct **230** is maximised with 2.1 equivalents of triethylamine (64%) (entry 3). We found that a further equivalent of base (i.e. 3.1 equivalents overall, entry 4) gave a very poor yield (16%) compared to incomplete neutralisation with 1.1 equivalents (42%) (entry 2). We decided to probe the influence of the nature of the base on the cycloaddition. No cycloaddition was observed when the triethylamine was replaced by 2.1 equivalents of DBU (entry 5), and a yield of only 10% was observed with potassium carbonate (entry 6).

Replacement of triethylamine with the more hindered analogue diisopropylethylamine afforded a yield of 44% with 1.25 equivalents of DMM (entry 7). This yield was increased to 52% by the use of 5 equivalents of DMM (entry 8).

Entry ^a	Base / equivs.	Equivs. of DMM	Yield of 230 (%)
1	Et ₃ N / 0	1.25	0
2	Et ₃ N / 1.1	1.25	42
3	Et ₃ N / 2.1	1.25	64
4	Et ₃ N / 3.1	1.25	16
5	DBU / 2.1	5	0
6	K ₂ CO ₃ / 2.1	1.25	10
7	ⁱ Pr ₂ NEt / 2.1	1.25	44
8	ⁱ Pr ₂ NEt / 2.1	5	52

a : All of these cycloaddition reactions were carried out at 60°C in toluene over 18 hours.

Table 3 : Effect of base on yield of cycloadduct 230.

Having decided upon 2.1 equivalents of triethylamine as the optimum, we resolved to use these conditions with various proportions of the dipolarophile (Table 4). We found significant differences between our best yield for 1.25 equivalents of DMM (64%) (Tables 3 and 4, entry 3) with those for 3 and 5 equivalents of DMM (40% and 57%) (Table 4, entries 9 and 10, respectively). We performed side-by-side reactions under strictly anhydrous conditions on 1.25 and 5 equivalents of DMM with rigorously purified reagents and solvents, to afford 46% and 49% yields, respectively (Table 4, entries 11 and 12). Thus, we

were able to conclude that the purity and dryness of the reagents were not key factors in determining the yield of our cycloaddition. We also ruled out the effect of adventitious moisture after experiments with 4Å and 5Å molecular sieves afforded poor yields of impure material (18% and 6%; entries 13 and 14 respectively).

Entry ^a	Equivs. DMM	Temp. (°C)	Time (h)	Yield of 230 (%)
3	1.25	60	18	64
9	3	60	18	40
10	5	60	18	57
11 ^b	1.25	60	18	46
12 ^b	5	60	18	49
13 ^c	1.25	60	18	18
14 ^d	1.25	60	18	6
15	1.25	60	4	25
16	1.25	60	8	38
17	1.25	60	24	25
18	1.25	60	40	27
19	3	90	18	0
20	5	90	18	0

a :All of these cycloaddition reactions were carried out in toluene with 2.1 equivalents of Et₃N over 18 h.

b : Rigorously purified and dried reagents. c : with 4Å molecular sieves. d : with 5Å molecular sieves.

Table 4 : Optimisation of cycloaddition reaction of 126a with DMM.

Increasing the cycloaddition reaction time was not revealing - 4, 24 and 40 hours at 60°C gave nearly identical yields (25%, 25% and 27%) (entries 15, 17 and 18, respectively). An 8 hour reaction time afforded 38% of **230** (entry 16), but did not challenge our optimum of 18 hours (entry 3). We found that no cycloadduct was formed when our best reaction conditions so far at 60°C (1.25 equivalents of triethyl orthoformate, 2.1 equivalents of Et₃N, 1.25 equivalents of DMM; Table 4, entry 3) were used at 90°C with 3 or 5 equivalents of DMM (entries 19 and 20) and so resolved to use 60°C or less in further optimisations.

Our modifications to the cycloaddition having been effective, we prepared to optimise the nitron formation step using our best cycloaddition conditions (2.1 equivalents Et₃N, 1.25 equivalents DMM, 60°C, 18 hours; Table 5, entry 3). We resolved to use 60°C in the nitron formation step, having observed reaction to completion inside 1 hour to isolate **126a** as the hydrochloride in quantitative yield and in high purity by HPLC analysis (Figure 22). The isolated yield of cycloadduct **230** after stirring **140a** and triethyl orthoformate for 3 hours at 60°C before effecting the cycloaddition was only 55% (Table 5, entry 21). A 6 hour reaction time reduced this yield to 46% (entry 22), and after 8 hours to 40% (entry 23).

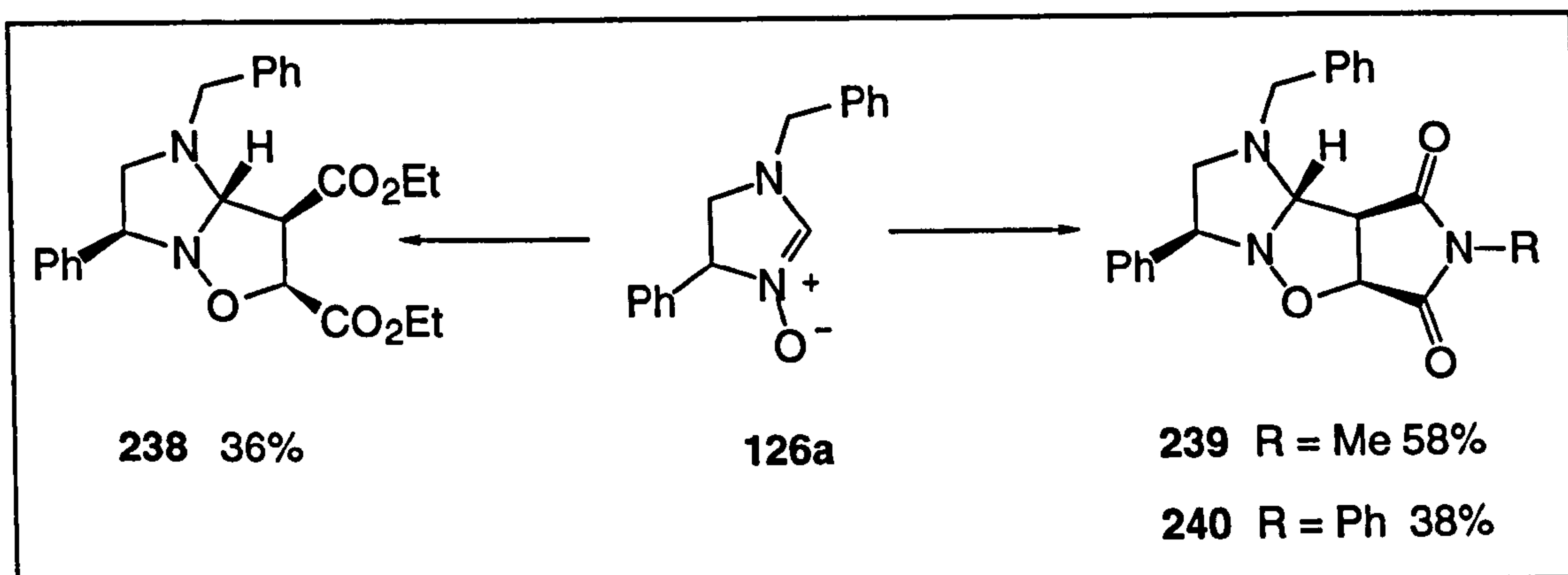
Having decided upon 1 hour as the optimum reaction time for formation of the nitron, we proposed to investigate the effect of the proportion of triethyl orthoformate. We approached our best yield to date (64%) (Table 5, entry 3) by the use of 3 equivalents of triethyl orthoformate (55%) (entry 24), and matched it by increasing the proportion to 5 equivalents (63%) (entry 25) or 10 equivalents (64%) (entry 26). We decided upon a final series of experiments with extended cycloaddition reaction times at 60°C and 20°C. A 1 hour nitron formation step with 10 equivalents of triethyl orthoformate at 60°C was thus followed by a 40 hour cycloaddition step with 1.25 and 5 equivalents of DMM to afford 39% and 59% of cycloadduct **230**, respectively (entries 27 and 28). Our optimisation was

completed by a similar experiment with a 24 hour cycloaddition at 20°C with 1.25 equivalents of DMM to afford the bicycle **230** in our best ever yield of 72% (entry 29). Thus, we found the optimum conditions for the nitron formation to be treatment of a slurry of dihydrochloride **140a** in anhydrous toluene with 10 equivalents of triethyl orthoformate at 60°C under nitrogen for 1 hour. The resultant solution then gives the highest yield of cycloadduct **230** (72%) when treated with 2.1 equivalents of Et₃N then 1.25 equivalents of DMM at 20°C and stirred for 24 hours.

	Nitron Formation			Cycloaddition		
Entry	HC(OEt) ₃ (equivs.)	Temp. (°C)	Time (h)	Temp. (°C)	Time (h)	Yield of 230 (%)
3	1.25	60	1	60	18	64
21	1.25	60	3	60	18	55
22	1.25	60	6	60	18	46
23	1.25	60	8	60	18	40
24	3	60	1	60	18	55
25	5	60	1	60	18	63
26	10	60	1	60	18	64
27	10	60	1	60	40	39
28 ^a	10	60	1	60	40	59
29	10	60	1	20	24	72

a : 5 equivalents of DMM; otherwise 1.25 equivalents. All reactions performed in dry toluene.

Table 5 : Nitron formation optimisation and final conditions.



Scheme 82

We followed up our success with DMM by reaction of the 2-H nitron **126a** with other symmetrical dipolarophiles containing a *cis* double bond (Scheme 82). These reactions and those that follow later in this section were performed by treatment of the hydroxylamino amine **140a** with 1.25 equivalents of triethyl orthoformate in toluene at 60°C for 1-2 hours before addition of 2.1 equivalents of triethylamine and 1.25 equivalents of DMM and stirring for 18-24 hours. They do not, therefore, reflect the optimised yield in each case. By this methodology, we were able to isolate the cycloadducts **238** of diethyl maleate (36%), **239** of N-methyl maleimide (58%) and **240** of N-phenyl maleimide (38%). Despite the decomposition of N-methyl maleimide cycloadduct **239** after extended periods in solution, its relative stereochemistry was assigned as for the previous cycloadduct by NOESY. Firstly, we confirmed the *cis*-relationship between the former maleimide protons H^a and H^b by observing their mutual enhancements (arrowed in Figure 26). Enhancements were observed between H^b and H^c and between H^c and H^d, allowing us to assign all three to one face of the cycloadduct. As expected, geminal protons H^d and H^e showed reciprocating enhancements, whilst H^e also enhanced H^f. Therefore, we were able to conclude that if H^a, H^b, H^c and H^d occupy the lower face of **239**, then H^e and H^f must occupy the upper face. In this case, we observed small enhancements between the bridgehead proton H^f and the

adjacent proton H^a which indicates their close proximity and might call into question our *trans* assignment. As for adduct **230**, there is no observable scalar coupling between H^f and H^a in the 1H NMR spectrum, suggesting a dihedral angle of approximately 90° which can only be achieved if H^f and H^a have a *trans* arrangement. Our assignment of the relative stereochemistry of **239** is thus consistent with the observations made for the dimethyl maleate cycloadduct **230** (Figure 23). The stereochemistry of cycloadducts **238** and **240** was thus assigned by comparison of their NMR data to that of **239**.

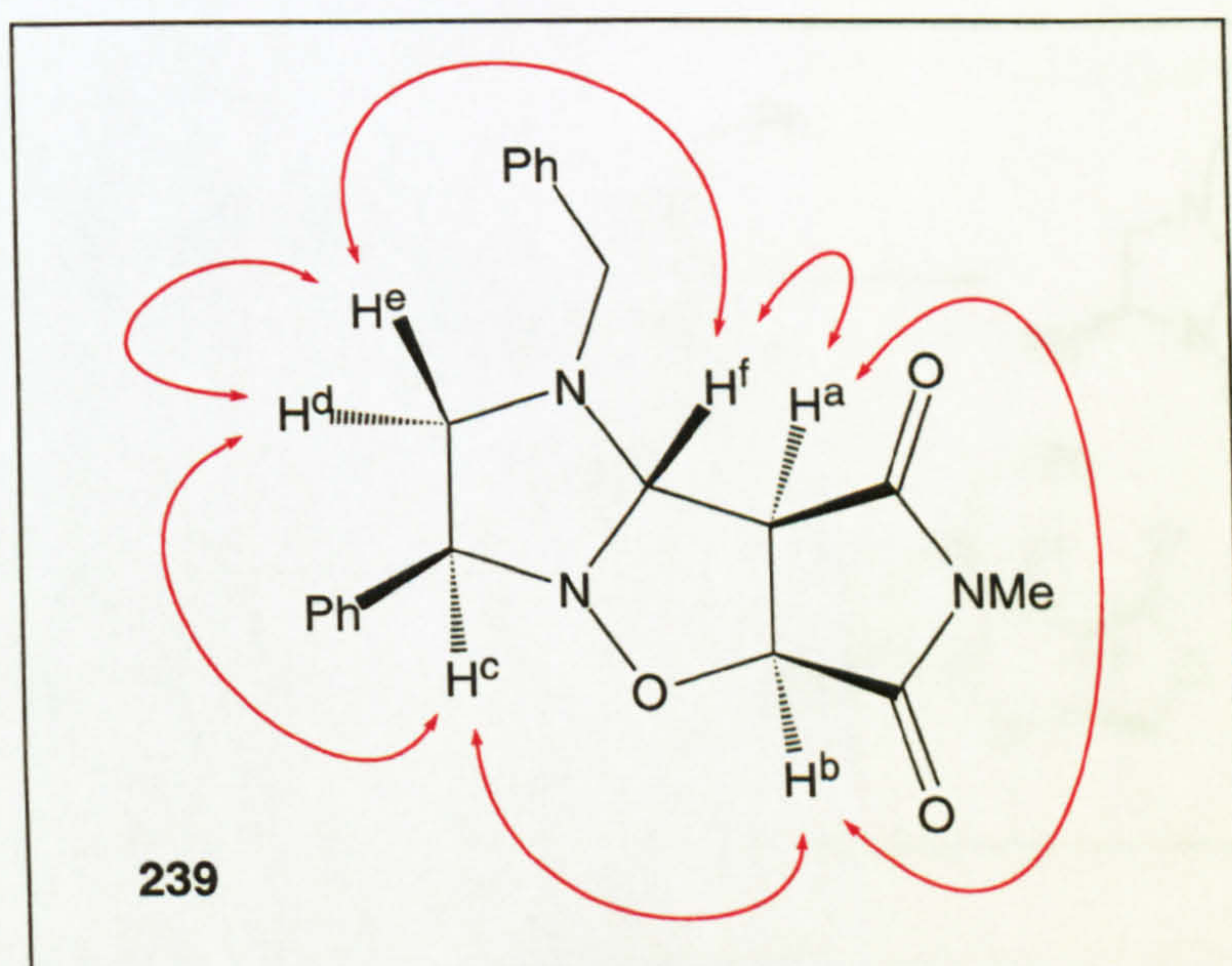
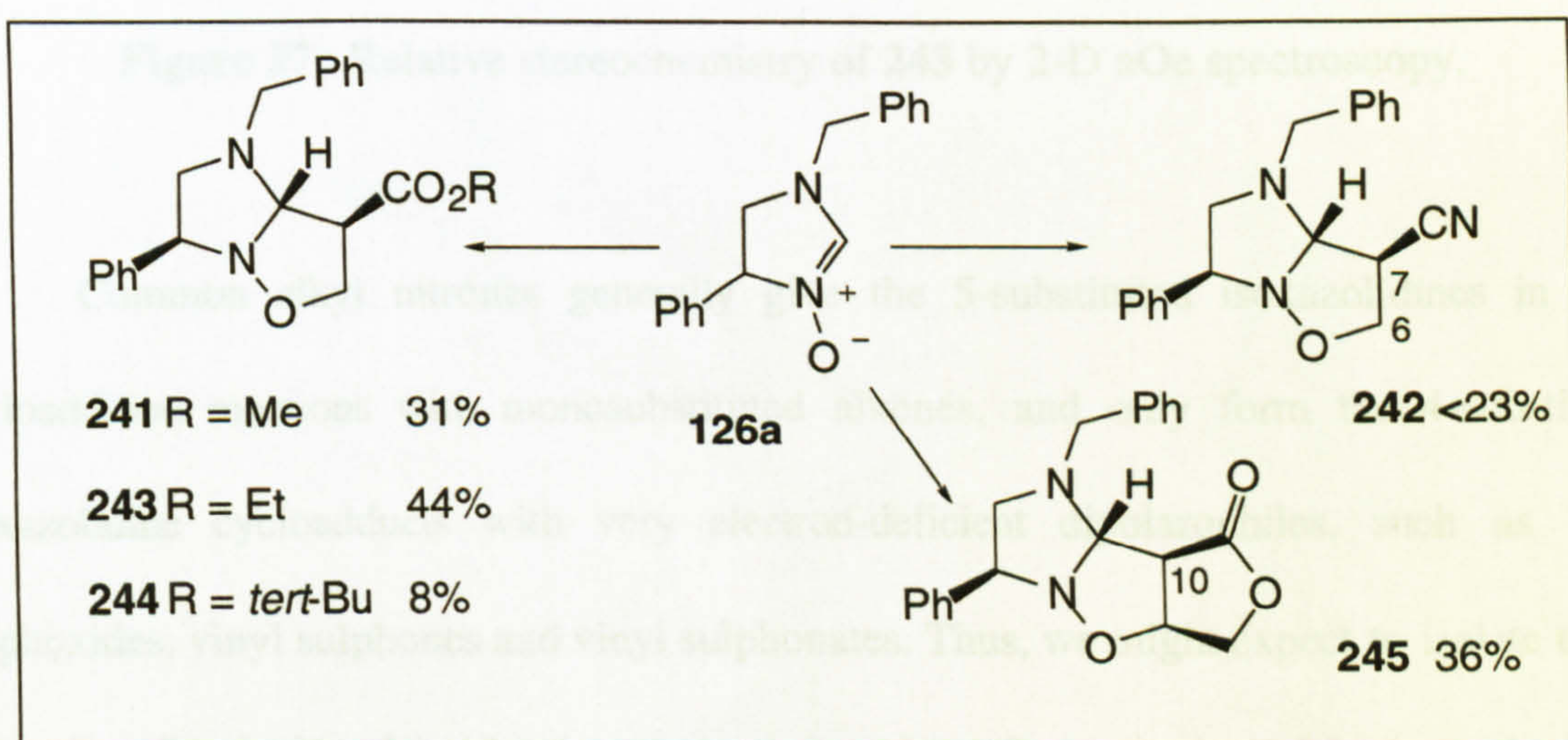


Figure 26 : Relative stereochemistry of **239** by 2-D nOe spectroscopy.

The next step for our studies was to investigate the regiochemical preference of **126a** by reaction with unsymmetrical alkene dipolarophiles. Thus, we reacted the nitron **126a** with methyl acrylate to afford the cycloadduct **241** (31%) (Scheme 83). Similarly, this reagent was reacted with other monosubstituted alkene dipolarophiles to prepare the cycloadduct **242** from acrylonitrile which was identified as the major component of an inseparable mixture on the basis of its similarity of its 1H NMR spectrum with other 7-substituted cycloadducts. In this way, we also prepared **243** from ethyl acrylate (44%) and

244 from *tert*-butyl acrylate (8%). It seems reasonable to speculate that the low yield of **244** reflects the effect on reactivity of accommodating the bulk of the *tert*-butyl moiety in the transition state. The regiochemical outcome was consistent in all of our reactions with mono-substituted alkenes, from which we only isolated the 7-substituted isoxazolidine cycloadducts. The reaction of 2(5*H*)-furanone with nitron **126a** also followed this pattern in that the electron-withdrawing ester substituent is found at the 10-position in the isoxazolidine ring of the isolated tricyclic cycloadduct **245** (36%).



Scheme 83

The relative stereochemistry of ethyl acrylate cycloadduct **243** was determined by NOESY (Figure 27). In this way, we were able to determine that H^a, H^b, H^c and H^d occupy one face of the cycloadduct whilst H^e and H^f occupy the other face. Again, whilst there is an observed enhancement between H^f and H^a, the zero coupling constant in the ¹H NMR again suggests a 90° dihedral angle and so a *trans* relationship. Comparison with the NMR data of adduct **243** has allowed the assignment of this same relative stereochemistry to the other cycloadducts in this series **241**, **242**, **244** and **245**.

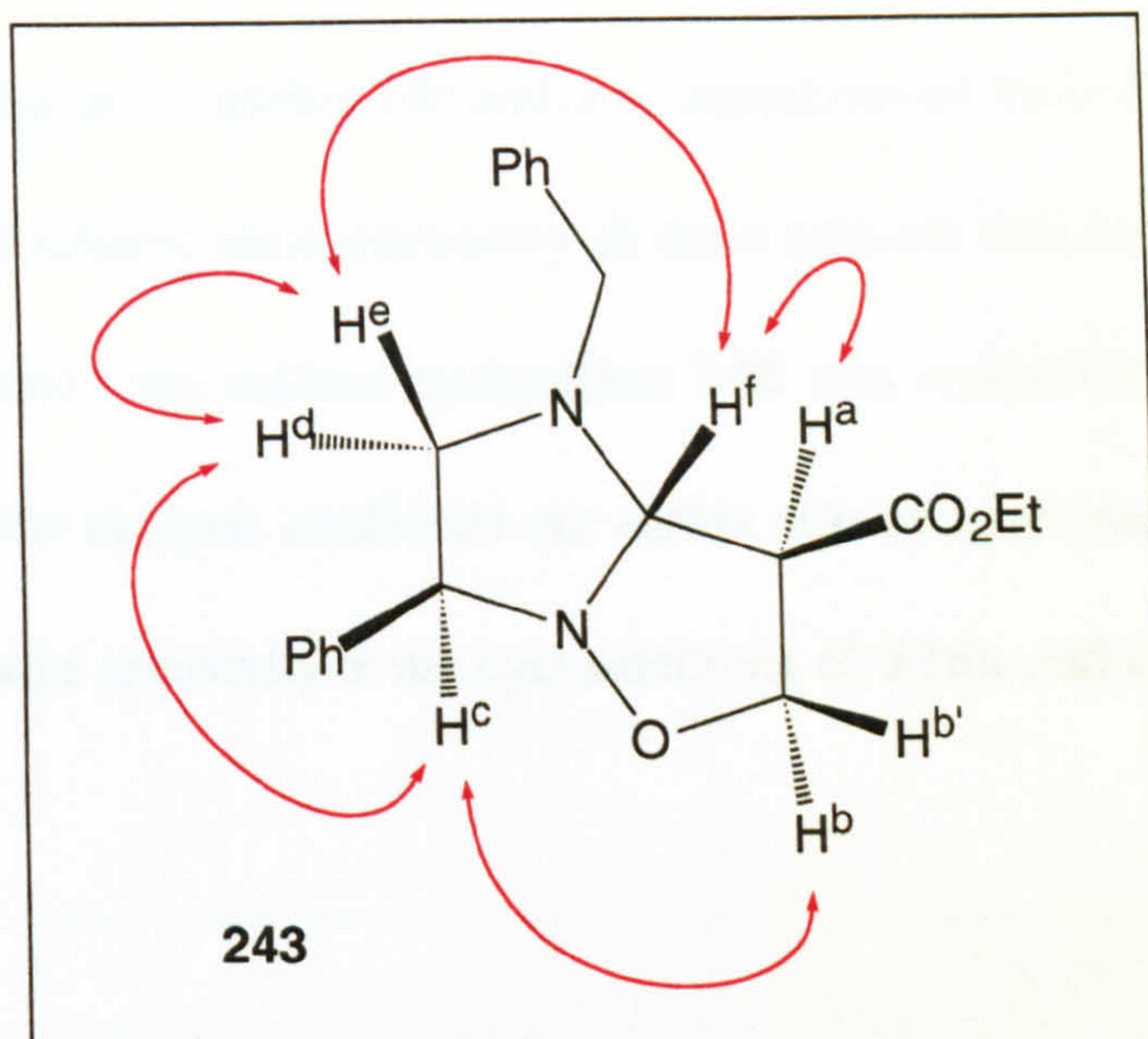


Figure 27 : Relative stereochemistry of **243** by 2-D nOe spectroscopy.

Common alkyl nitrones generally give the 5-substituted isoxazolidines in their cycloaddition reactions with monosubstituted alkenes, and only form the 4-substituted isoxazolidine cycloadducts with very electron-deficient dipolarophiles, such as vinyl sulphoxides, vinyl sulphones and vinyl sulphonates. Thus, we might expect to isolate the 6- rather than 7-substituted imidazoisoxazole cycloadducts from reaction of **126a** with all but the most electron-deficient dipolarophiles. However, **126a** has shown total regioselectivity with moderately electron-deficient dipolarophiles and those dipolarophiles with exaggerated electron-deficiency should only serve to enhance the demonstrated proclivity of our nitron **126a** to form 7-substituted imidazoisoxazole cycloadducts.

We isolated cycloadduct **246** from the reaction of **126a** with methyl vinyl sulfone (46%), **247** from ethyl vinyl sulfone (32%), and **248** from phenyl vinyl sulfone (49%) (Scheme 84). Again, the regioselectivity is complete; the 7-substituted imidazoisoxazoles are the only isolated products. The assignment of the relative stereochemistry of the methyl vinyl sulfone adduct **246** was made by NOESY. As before, the bridgehead proton H^f enhances the adjacent proton H^a (α - to the sulfone) but with a zero coupling constant. The other

enhancements are also as for adduct **243** and, by comparison of these NMR data with those for **247** and **248**, the relative stereochemistry of these adducts was assigned as previously. In addition, the phenyl vinyl sulfone cycloadduct **248** was crystallised from methanol and X-ray crystallographic analysis confirmed our earlier nOe assignments (Figure 28). Again, we observed total facial selectivity in the cycloadditions of **126a** and total selectivity for the *exo* product.

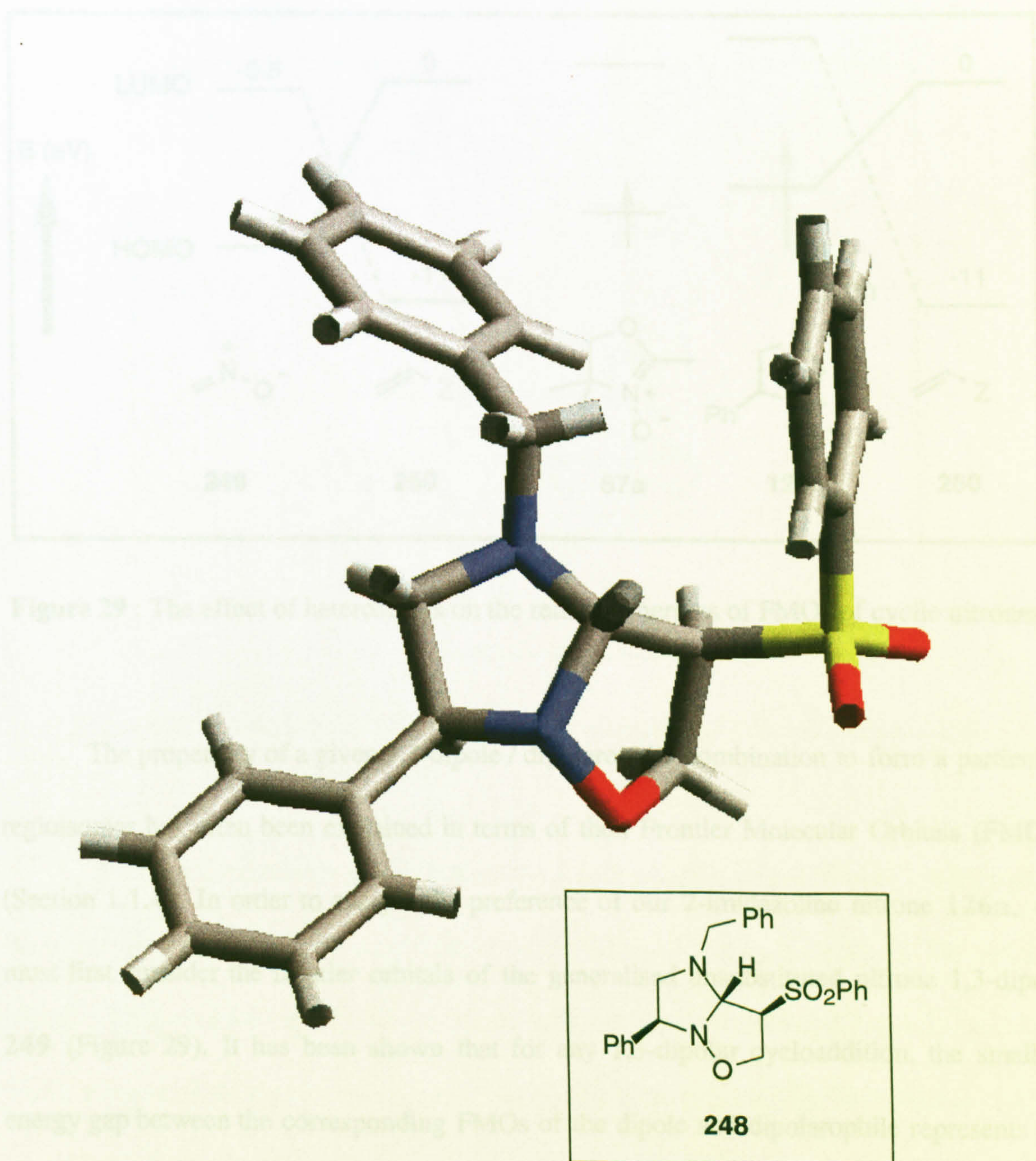
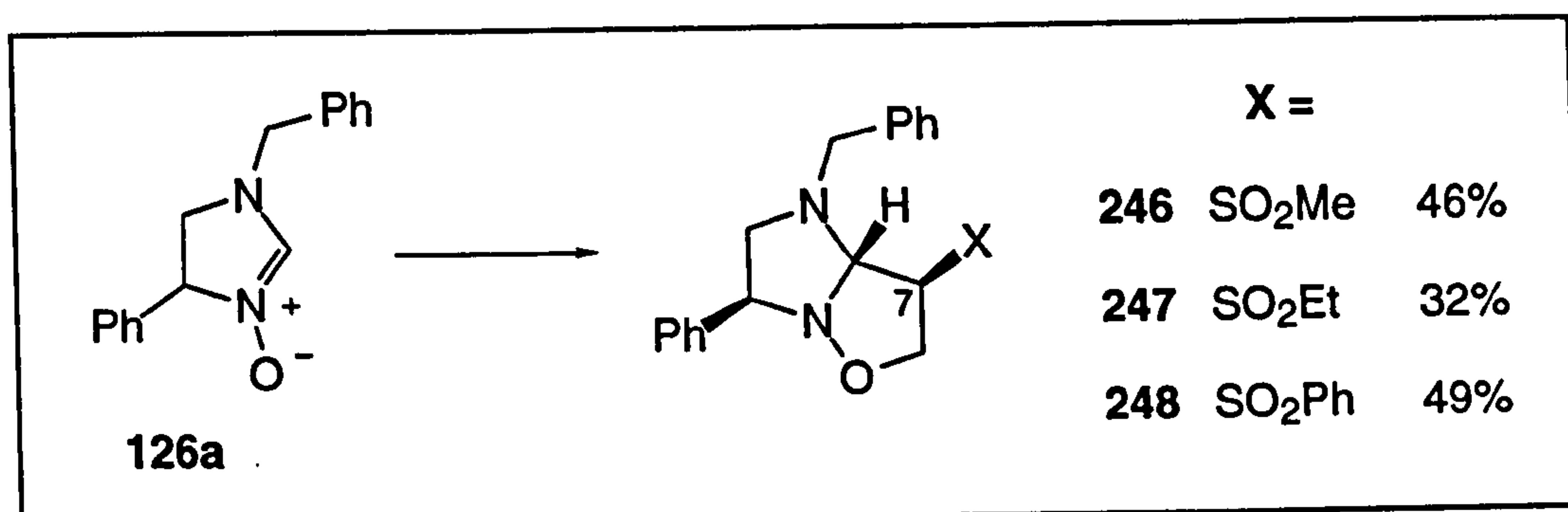


Figure 28 : X-ray crystal structure of **248**.



Scheme 84

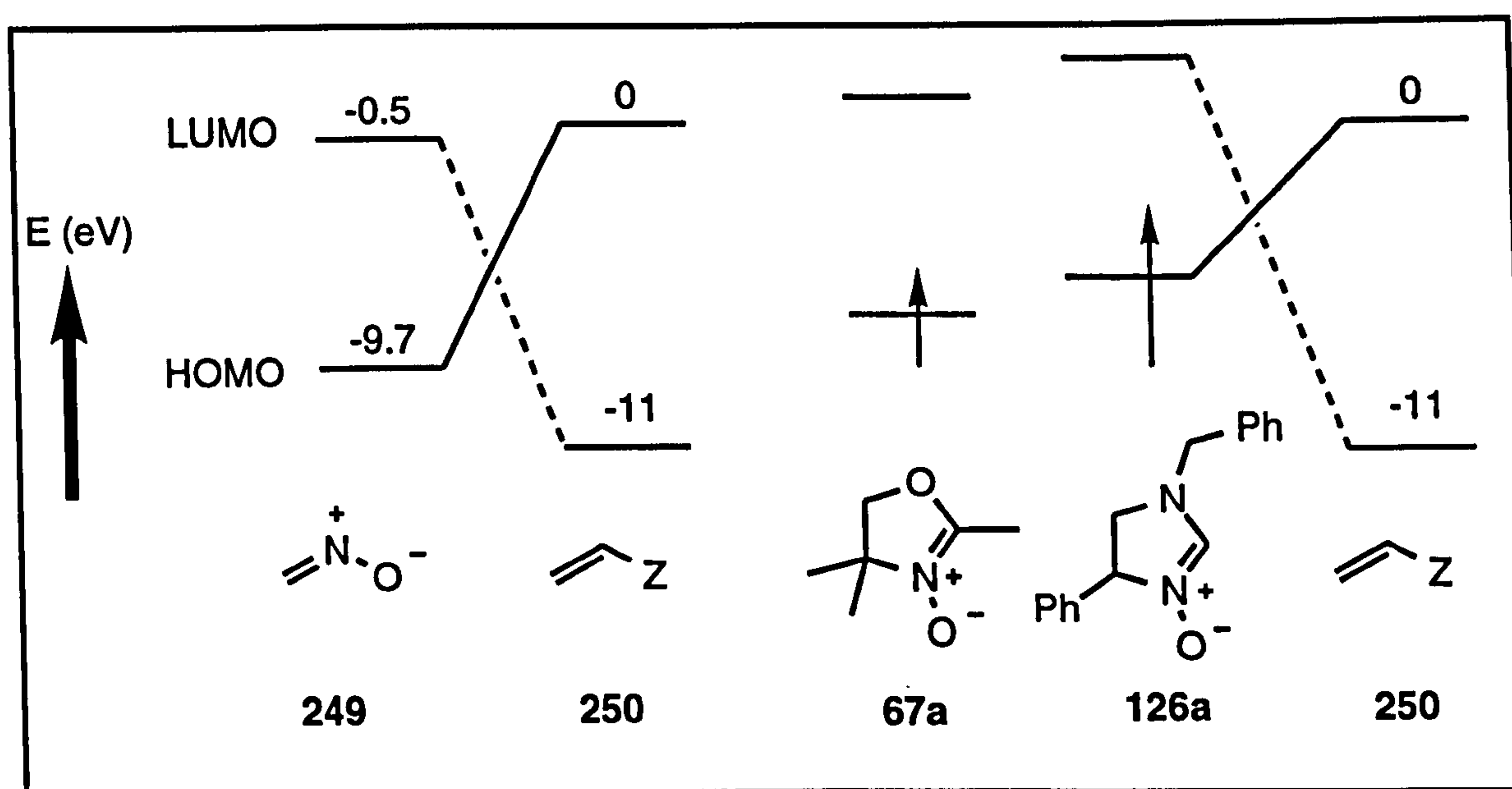


Figure 29 : The effect of heteroatoms on the relative energies of FMOs of cyclic nitrones.

The propensity of a given 1,3-dipole / dipolarophile combination to form a particular regioisomer has often been explained in terms of their Frontier Molecular Orbitals (FMOs) (Section 1.1.4). In order to analyse the preference of our 2-imidazoline nitron **126a**, we must first consider the frontier orbitals of the generalised unsubstituted nitron 1,3-dipole **249** (Figure 29). It has been shown that for any 1,3-dipolar cycloaddition, the smallest energy gap between the corresponding FMOs of the dipole and dipolarophile represents the optimum orbital overlap and therefore the fastest reaction (Section 1.1.4). The relative energies of the HOMO and LUMO of many classes of 1,3-dipole, including the

unsubstituted nitrone **249**, have been calculated.²¹ Comparison of the relative energy of these FMOs with those calculated for an alkene dipolarophile **250** bearing an electron-withdrawing substituent Z,²¹ clearly shows that the dipole HOMO-dipolarophile LUMO interaction has the smallest energy gap. As this is the strongest bonding interaction, the reaction should be dipole HOMO controlled and constitutes a Type I interaction in the notation proposed by Sustmann (Section 1.1.4) (Figure 29).²⁴

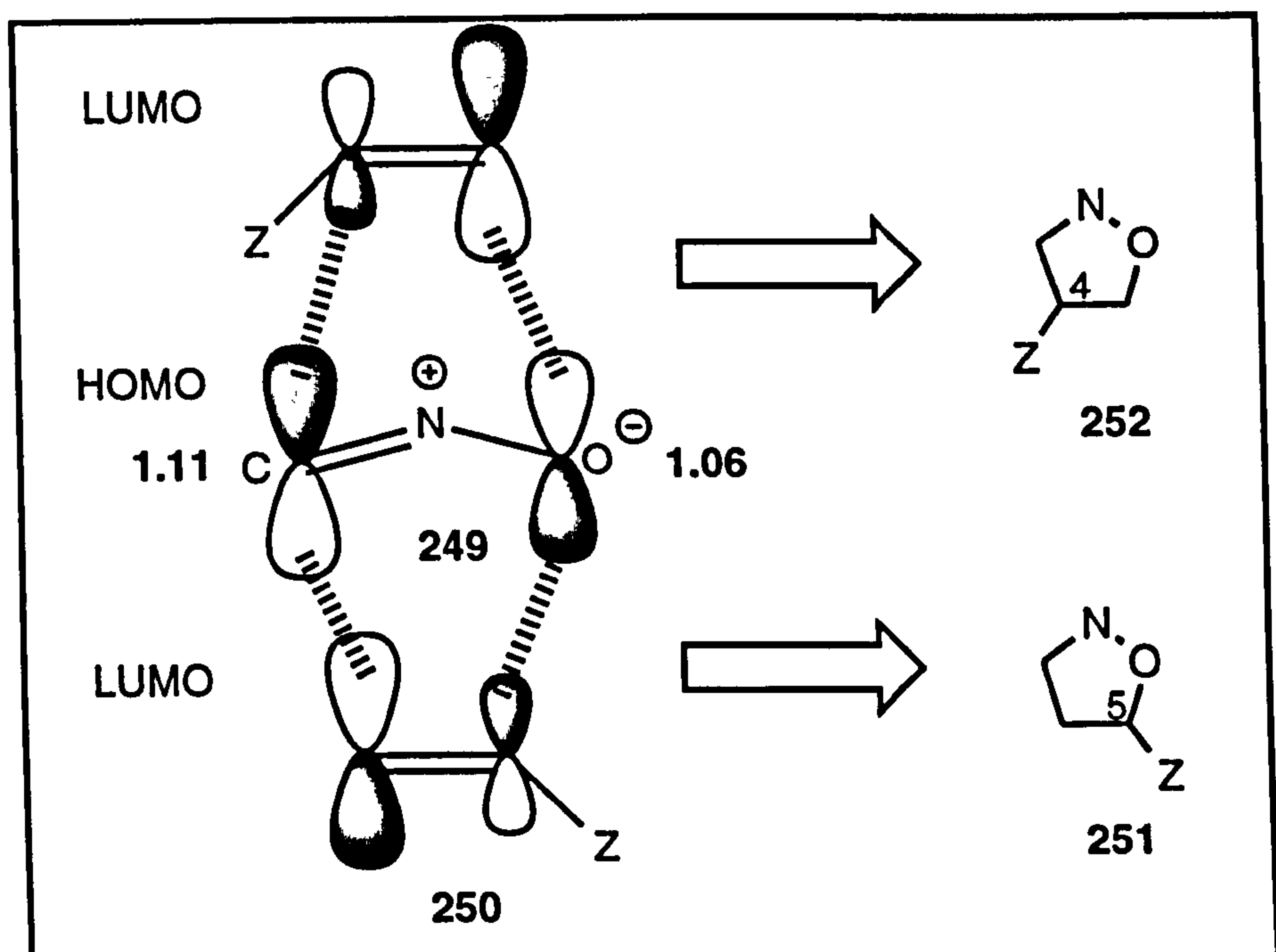


Figure 30 : Nitron HOMO control affords mixed isoxazolidine cycloadducts.

The orbital interaction is greatest between orbitals with similar orbital coefficients at the interacting atoms, in other words, small with small and large with large.²¹ The terminal orbital coefficients for the HOMO of nitrone **249** are nearly identical (C = 1.11 and O = 1.06), and so neither regioisomer is preferred on this basis (Figure 30). Thus, dipole HOMO control will lead to a mixture of 4- and 5-substituted isoxazolidine cycloadducts.²¹ In this case, the regiochemistry of addition is decided by the weaker interaction of the dipole LUMO and dipolarophile HOMO. Here, the nitrone LUMO coefficients differ significantly (C =

0.98 and O = 0.32), and so a much stronger bonding interaction can occur in the orientation for which the orbital coefficients are matched. Thus, the cycloaddition reactions of unsubstituted nitrones **249** most often proceed *via* apparent dipole LUMO control to give the 5-substituted isoxazolidine product **251** rather than the 4-substituted cycloadduct **252** for which the coefficients are mis-matched (Figure 31).

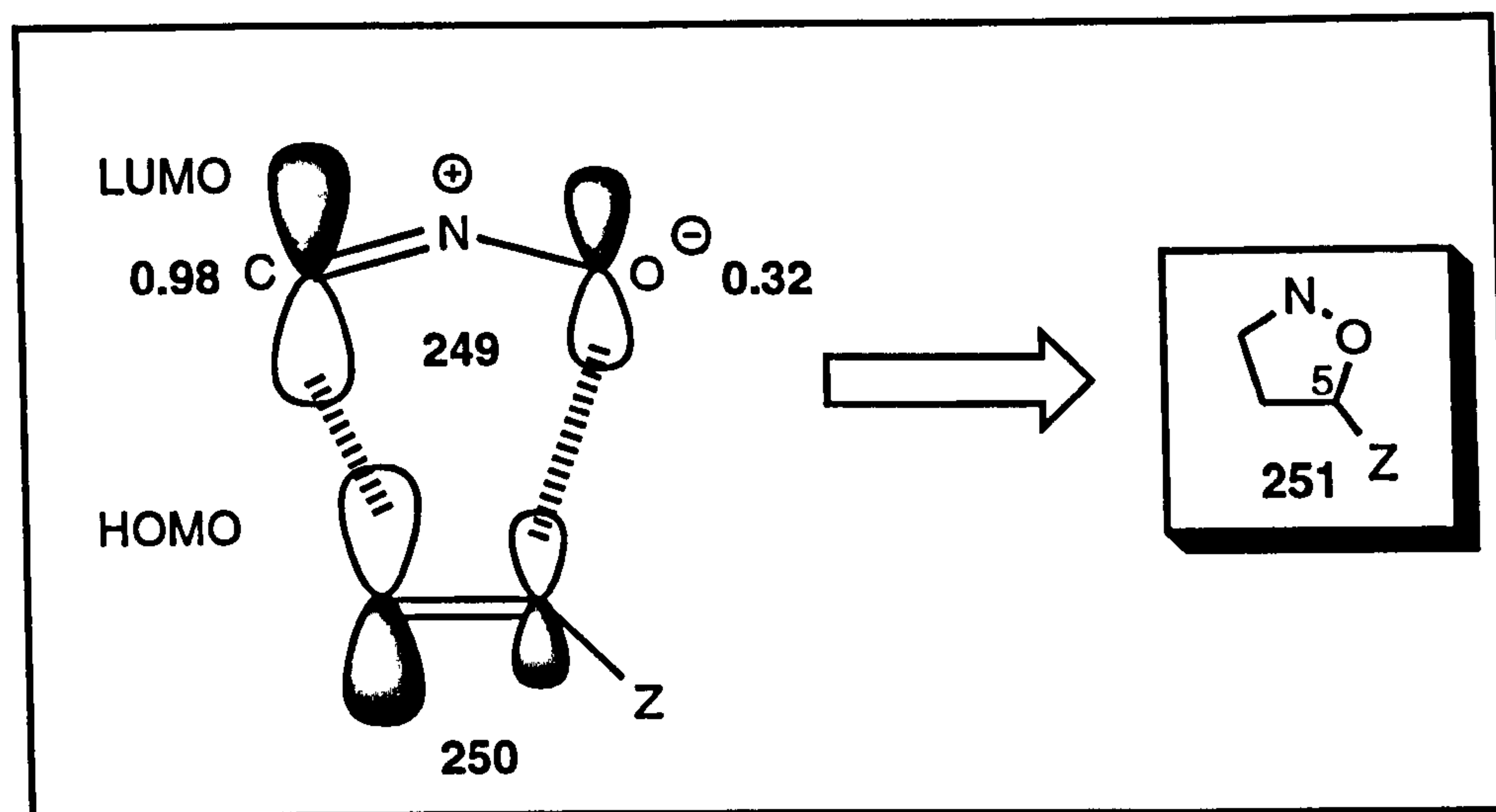
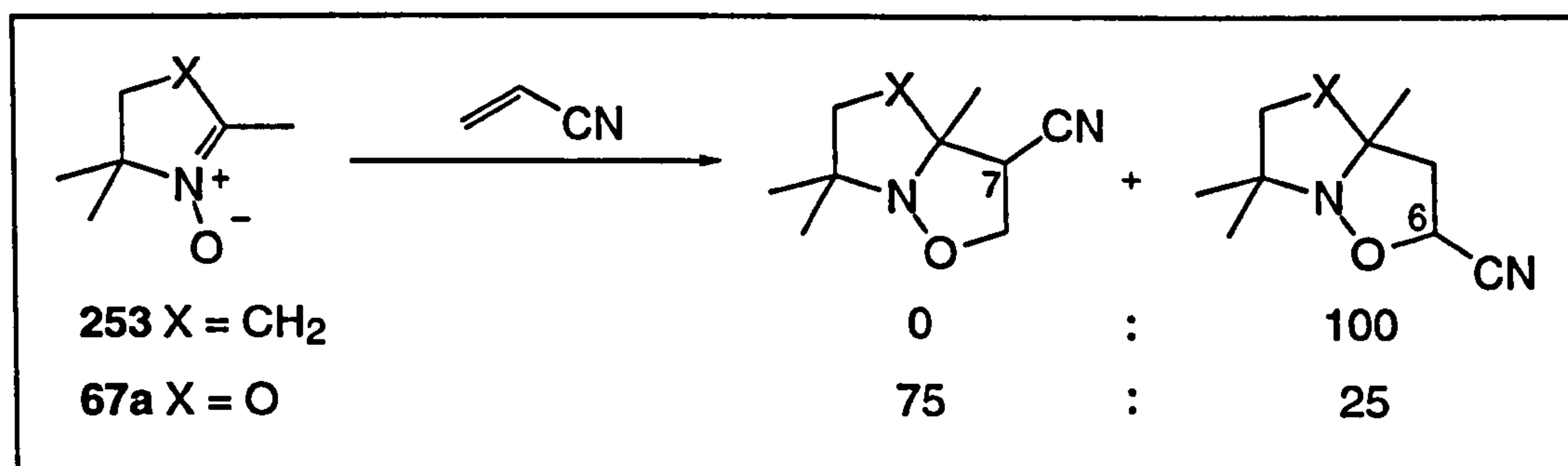


Figure 31 : Nitron LUMO control affords 5-substituted isoxazolidines.

If we substitute at the nitron carbon with a conjugating donor nitrogen atom, we would expect to increase the energy of both the dipole HOMO and LUMO (Figure 29). Thus, we might predict that the energy gap between the HOMO of the dipole **126a** and the LUMO of an electron-deficient dipolarophile **250** would be sharply reduced and the cycloaddition reactions of these dipoles should be strongly HOMO controlled. Whereas the unsubstituted nitron **249** offers little difference in the terminal orbital coefficients, the presence of the nitrogen atom at the nitron α -carbon of **126a** will strongly enhance the dipole HOMO orbital coefficient on oxygen.²¹ This new polarisation should now allow the dipole HOMO to determine the regiochemistry of the product and so the 4-substituted isoxazolidine should predominate. Thus, by FMO theory we expect to isolate the 7-

substituted imidazoisoxazole cycloadducts with our 2-H nitron **126a** rather than the 6-substituted regioisomers. Our hypothesis is supported by the regiochemical preference shown by the related oxazoline nitron **67a** developed by Coates and Ashburn.⁹⁹ They observed total selectivity for the 6-substituted isoxazolopyrrole* in the cycloaddition of the pyrrolidine nitron **253** with acrylonitrile, as predicted by FMO theory (Scheme 85). This selectivity was reversed (7-:6-substitution* = 3:1) after the introduction of an oxygen atom at the nitron α -carbon to give the oxazoline nitron **67a**.

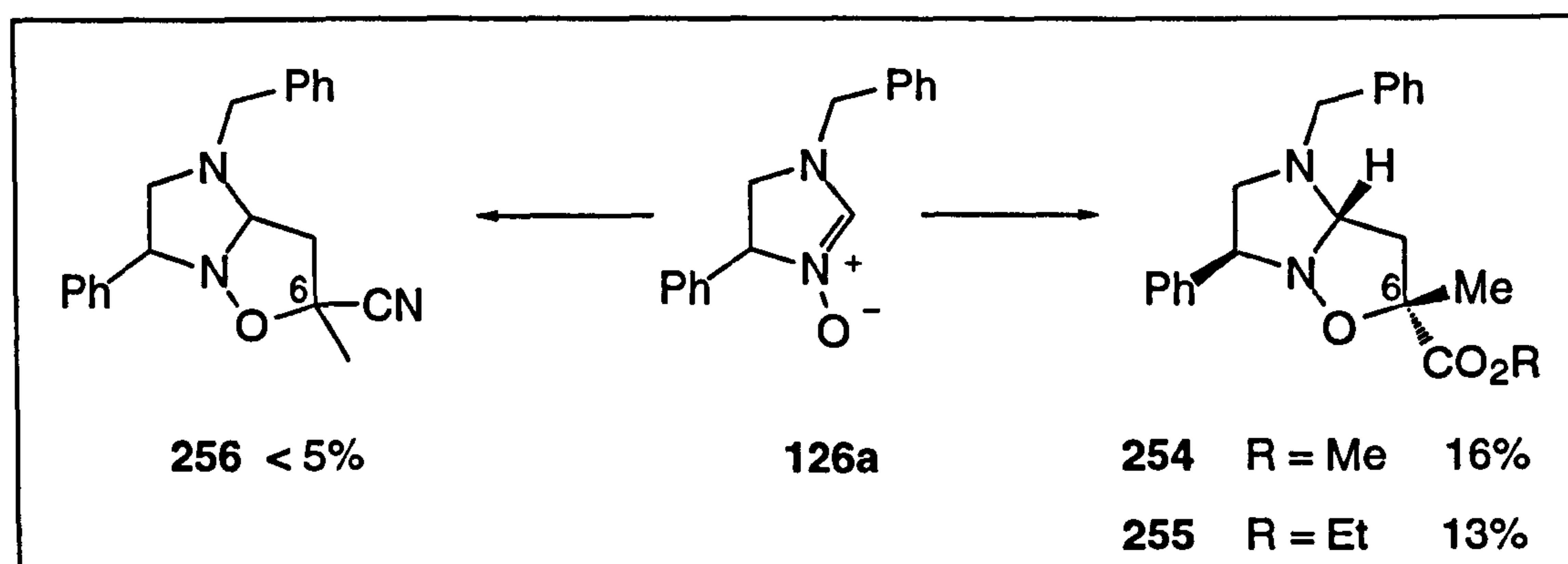


* Both the isoxazolopyrrole and oxazoloisoxazole rings are numbered according to the latter for clarity.

Scheme 85

Study of the cycloadditions of our 2-imidazoline nitron **126a** with 1,1-disubstituted alkenes began with methyl methacrylate, which afforded the 6,6-disubstituted imidazoisoxazole **254** (16%) as the only observed cycloadduct, (Scheme 86). Similarly, we reacted **126a** with ethyl methacrylate to afford cycloadduct **255** (13%) and with methacrylonitrile to afford **256** (<5%) which was assigned from a mixture by comparison of its ¹H NMR data with **254** and **255**. Here, the regiochemical preference of nitron **126a** for 7-substituted adducts is overturned and it is clear that the frontier orbitals are no longer enforcing regiocontrol. This reversal of regiochemistry and associated poor yields are probably the result of the increased steric bulk of these 1,1-disubstituted dipolarophiles. No

longer able to approach the imidazoline ring without unfavourable steric clash, it seems that the 1,1-disubstitution pattern is better accommodated by the exocyclic position of the nitron oxygen and so the 6,6-disubstituted products predominate. The relative stereochemistry of **254** was assigned by NOESY and it is clear that this cycloadduct is formed *via* the transition state in which the ester functionality is *endo*, and we have assigned **255** and **256** in this way.



Scheme 86

The reaction of the 2-H nitron **126a** with ethyl vinyl ether **257** failed to produce any 1,3-dipolar cycloadduct (Figure 32). Similarly, no cycloaddition was observed with vinyl trimethylsilane **258** or vinyl acetate **259**, suggesting that this nitron is not reactive towards electron-rich dipolarophiles. Styrene **260** likewise produced no sign of an isoxazolidine with **126a**, allowing us to reason that alkenes substituted with conjugating groups are also ineffective dipolarophiles here. The failure to observe any cycloadduct with maleic anhydride **261** may be tentatively attributed to the instability of the cycloadduct to hydrolysis, producing highly polar zwitterionic material which would be difficult to isolate. We might expect the cycloaddition reactions of more reactive dipolarophiles to compete with unwanted side-reactions, but no cycloadducts were observed in the reaction of **126a** with

dimethyl azodicarboxylate or phenyl isocyanate. Other electron-deficient dipolarophiles for which no cycloaddition was observed included 5,6-dihydro-2*H*-pyran-2-one **262**, 2,2-dimethyl-3(2*H*)-furanone **263**, vinyl acrylate **264**, acrylamide **265**, methyl vinyl ketone **266**, phenyl methacrylate **267** and Tuppy's maleimide **268**.

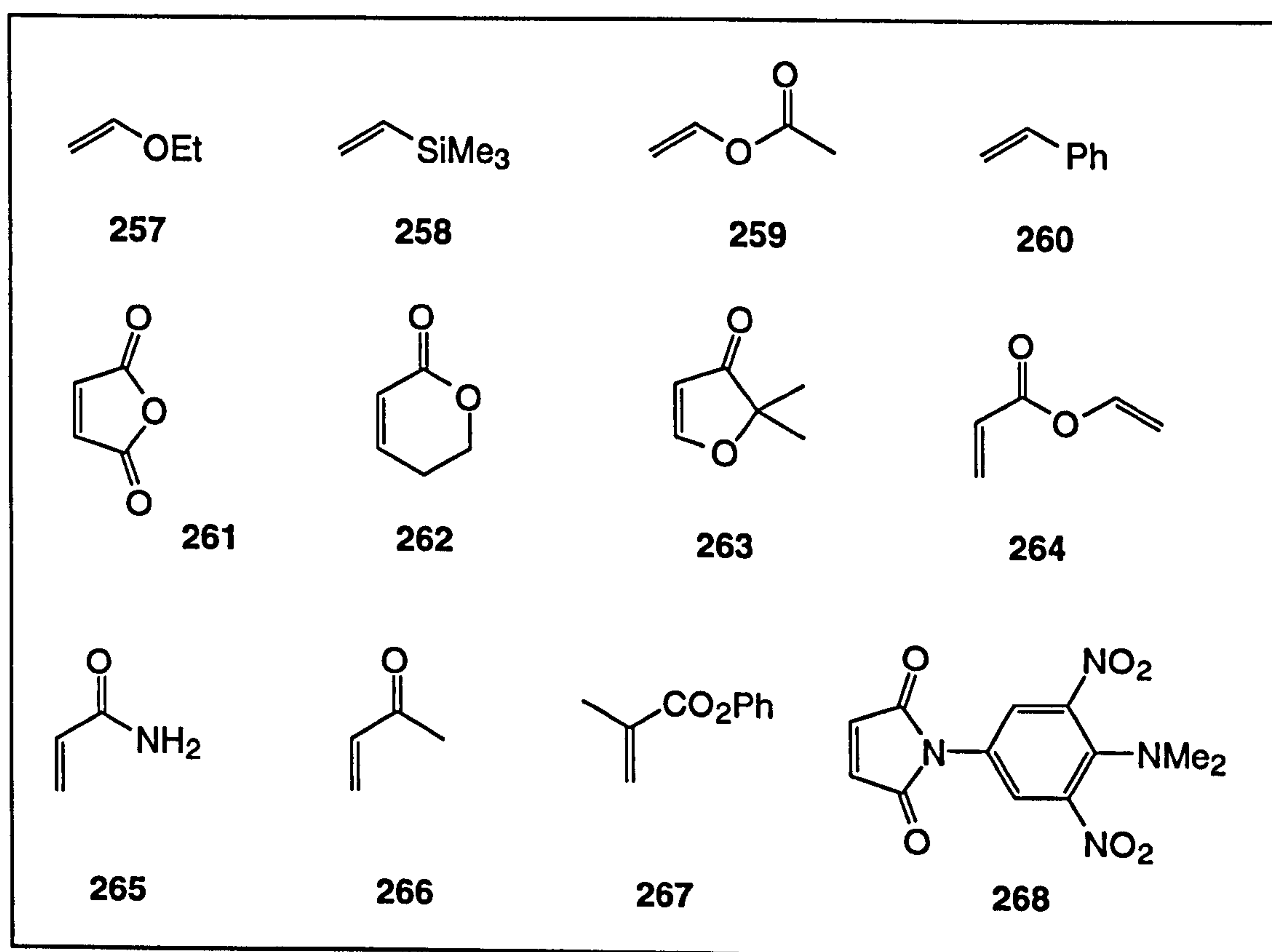
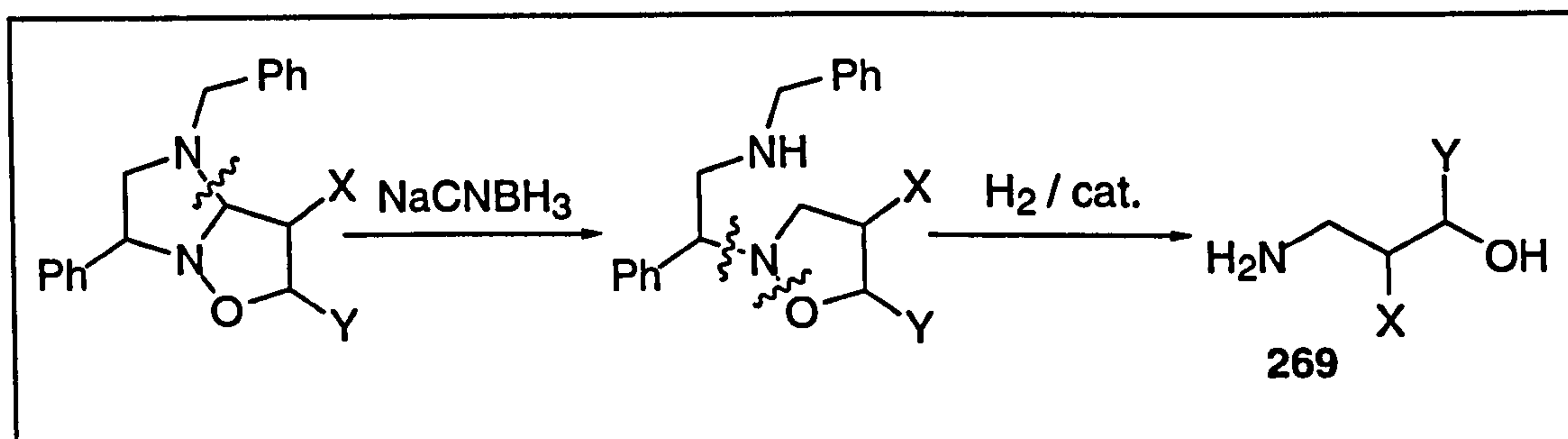


Figure 32

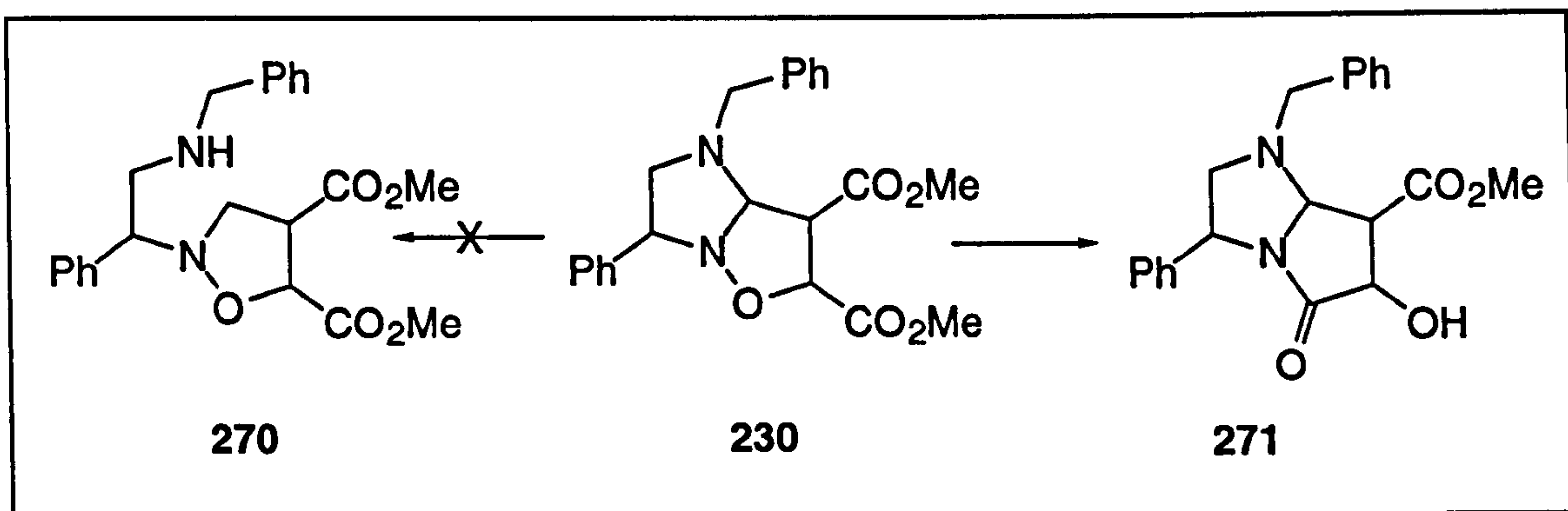
2.4 Progress towards a template removal strategy

The planned template removal strategy began with a sodium cyanoborohydride reduction of the aminal functionality. It was hoped that it would then be possible to perform simultaneous catalytic hydrogenolysis of the N–O bond of the isoxazolidine and the N-benzyl moiety of the template to afford functionalised amino alcohols **269** (Scheme 87) or cyclisation products derived from them.



Scheme 87

It was decided that the dimethyl maleate cycloadduct **230** should be taken forward into the template removal phase as it offered the highest cycloaddition yields and the greatest potential for later functionalisation. However, this cycloadduct was unreactive to NaCNBH_3 at pH 4 in ethanolic solution, or glacial acetic acid at 20°C , returning unchanged starting material after lengthy reaction times. A similar experiment in which the solution was heated to 60°C for 1.5 hours, showed some consumption of the cycloadduct but none of the desired isoxazolidine **270** was isolated from the resultant mixture. We were also unsuccessful in attempts to reduce cycloadduct **230** with NaBH_4 or LiAlH_4 at 20°C , or with $\text{BH}_3\cdot\text{THF}$ at 20°C or at reflux.



Scheme 87

As the amination reduction presumably depends upon the availability of the lone pair on the isoxazolidine nitrogen (to generate an amino-iminium salt), we decided to cleave the N–O bond and thus facilitate the participation of these electrons. The hydrogenolysis of the N–O bond of isoxazolidines with common, commercial catalysts is well documented in the literature.²⁸⁵⁻²⁸⁷ The cycloadduct **230** was therefore subjected to atmospheric pressure hydrogenolysis with 5mol% of 5% Pd-C at 30°C for 18 hours to afford the lactam **271** (13%) (Scheme 88). This product is consistent with the expected N–O cleavage followed by spontaneous lactamisation of the secondary amino function. However, this lactam was not isolated from such reaction at room temperature even in the presence of a drop of conc. HCl, nor in acid-free solution with 5mol% of 10% Pd-C. Atmospheric pressure hydrogenolysis at 50°C, and hydrogenolysis at 50psi of H₂ at 20°C, were also unsuccessful.

A reagent we had intended to use for simultaneous N–O cleavage and debenzoylation was Pearlman's catalyst (palladium(II) hydroxide). Hydrogenolysis at ambient temperature and pressure with this catalyst, however, gave our best yield of the lactam **271** to date, albeit a modest 27%. At the same time we were exploring other catalysts and conditions of which 10% Pd-BaSO₄ was the first, but this returned the starting material unchanged after 18 hours, as did 5% Pt-C, PtO₂, 5% Rh-C or 5% Ru-C, either at ambient or elevated pressure.

We extended our search to the less usual reagents and methods, looking to Birch reduction with sodium metal in liquid ammonia,²⁸⁸ and catalytic transfer hydrogenation with 10% Pd-C and ammonium formate,^{241,289} as well as extended reflux with zinc and acetic acid but all were unsuccessful. Langlois *et al.* have developed a method for isoxazolidine cleavage using *m*-CPBA in which a nitron is regenerated and hydrolysed with dilute acid to yield the corresponding aldehyde.¹⁰² However, we found no evidence for the formation of the desired aldehyde from bicycle **230**. We were similarly unsuccessful in our attempts to apply the chemistry of van Boggelen *et al.*, in which N-O lysis is achieved *via* N-methylation with MeI in THF.²⁸⁶ Literature precedent exists for the cleavage of N-O bonds in isoxazoles, isoxazolines and isoxazolidines with metal-carbonyl complexes.²⁹⁰⁻²⁹² Isoxazolidine **230** was heated at reflux in moist acetonitrile for 30 minutes with molybdenum hexacarbonyl, to give a dark brown gum possibly consistent with the complex of cycloadduct **230** and Mo(CO)₆, but not the desired ring-cleaved product or the lactam **271**.

We were encouraged by literature precedent to try high-pressure hydrogenation with commercial Raney nickel (analogous to W-2 or Raney 28), but found the amount of catalyst used to vary greatly between experimenters.^{240,293} After 18 hours at 60psi of H₂ with 0.5 equivalents w/w of catalyst, the starting material was unchanged, and so an additional 4 equivalents were added before agitating at 60psi for a further 18 hours. Chromatographic purification of the resulting mixture afforded the desired lactam **271** as a white crystalline solid (19%) and encouraged further optimisation. As hydrogenation apparatus that would tolerate significantly increased pressures was not readily available, we looked to varying the solvent as well as the proportion and activity of the catalyst. At 2 equivalents of Raney nickel w/w we isolated the lactam **271** in a yield of 32-42% after chromatography. All experiments thus far had been conducted in methanol, but we observed no improvement in yield by

hydrogenation in ethanol or ethyl acetate (25% and 0%, respectively). Reaction with 3 equivalents of catalyst gave the lactam in a yield of 59%, but this was slightly bettered by reaction with 12 equivalents to afford 66% of **271**. We prepared a sample of nickel catalyst by the Raney method from nickel-aluminium amalgam, washing out the aluminium with aqueous sodium hydroxide. Whilst this material seemed highly active, to the point of spontaneous ignition in air, the 39% yield of the lactam **271** did not challenge that of the commercial catalyst.

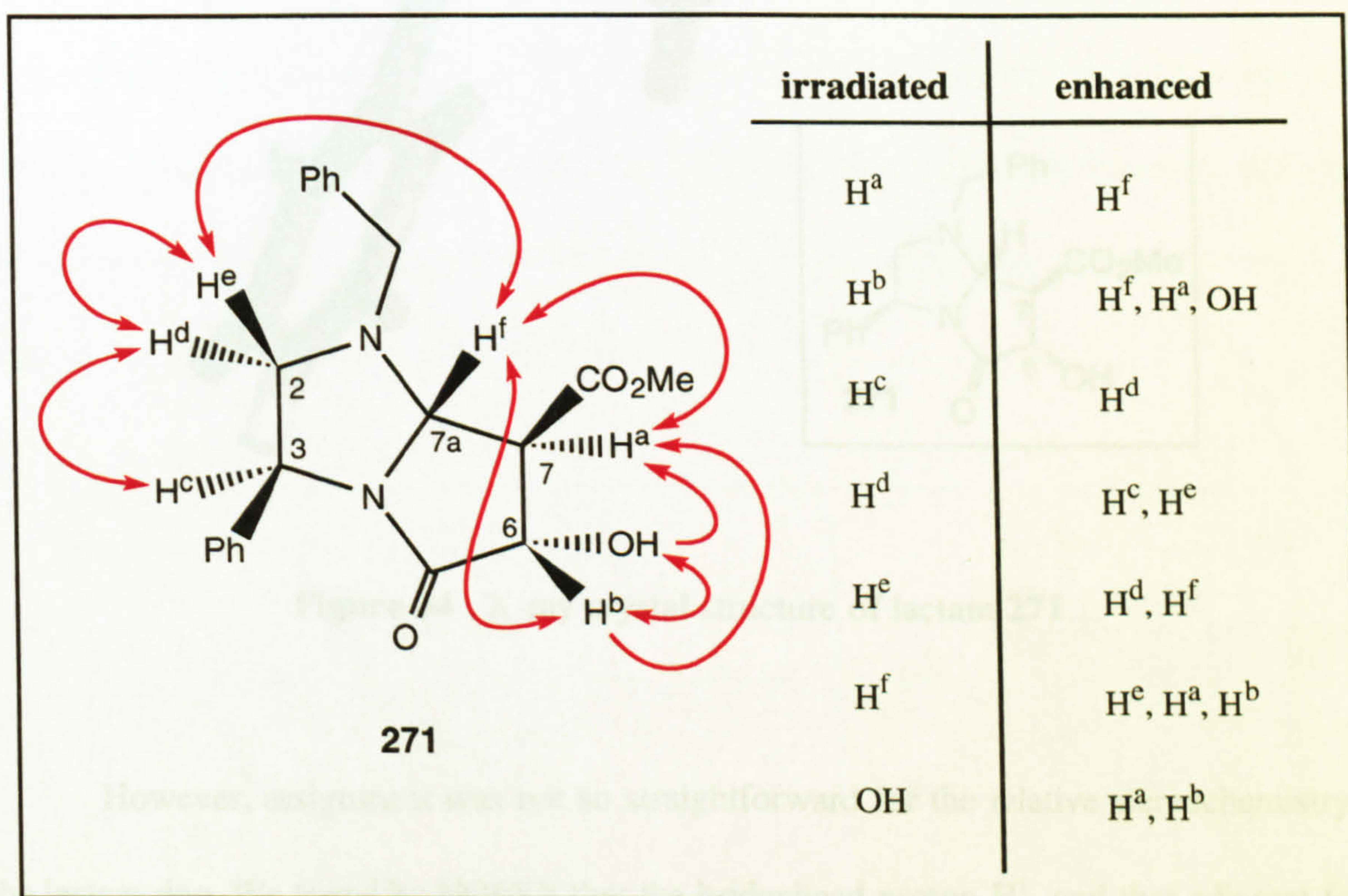


Figure 33 : Nuclear Overhauser enhancements for lactam **271**

Qualitative difference nOe experiments allowed reliable assignment of the relative stereochemistry of the imidazoline ring of the lactam **271**; enhancements were observed in both directions between H^c and H^d, H^d and H^e as well as H^e and H^f (Figure 33). Thus we were able to conclude that if H^c and H^d shared the lower face then H^e and H^f shared the upper face.

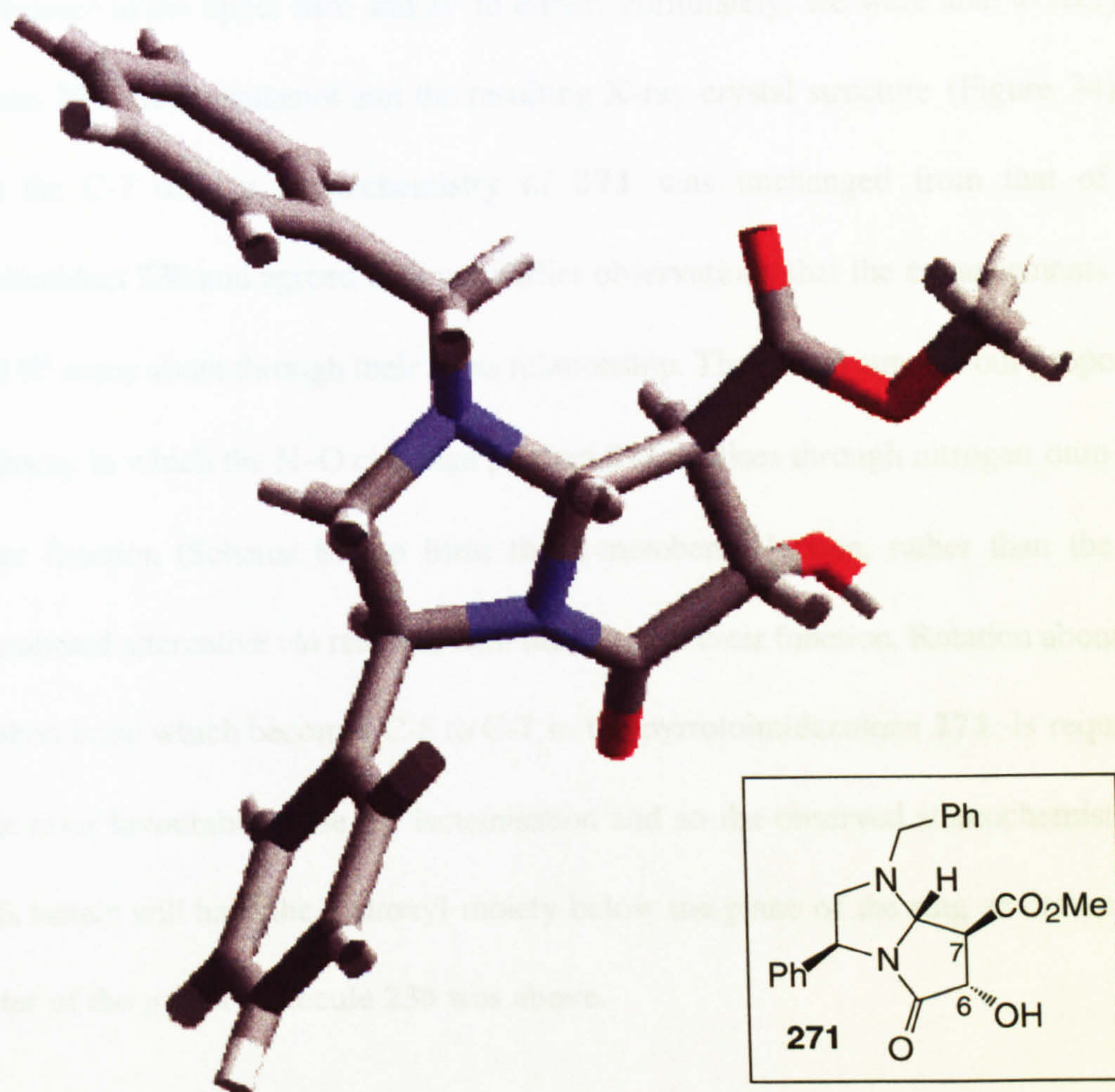
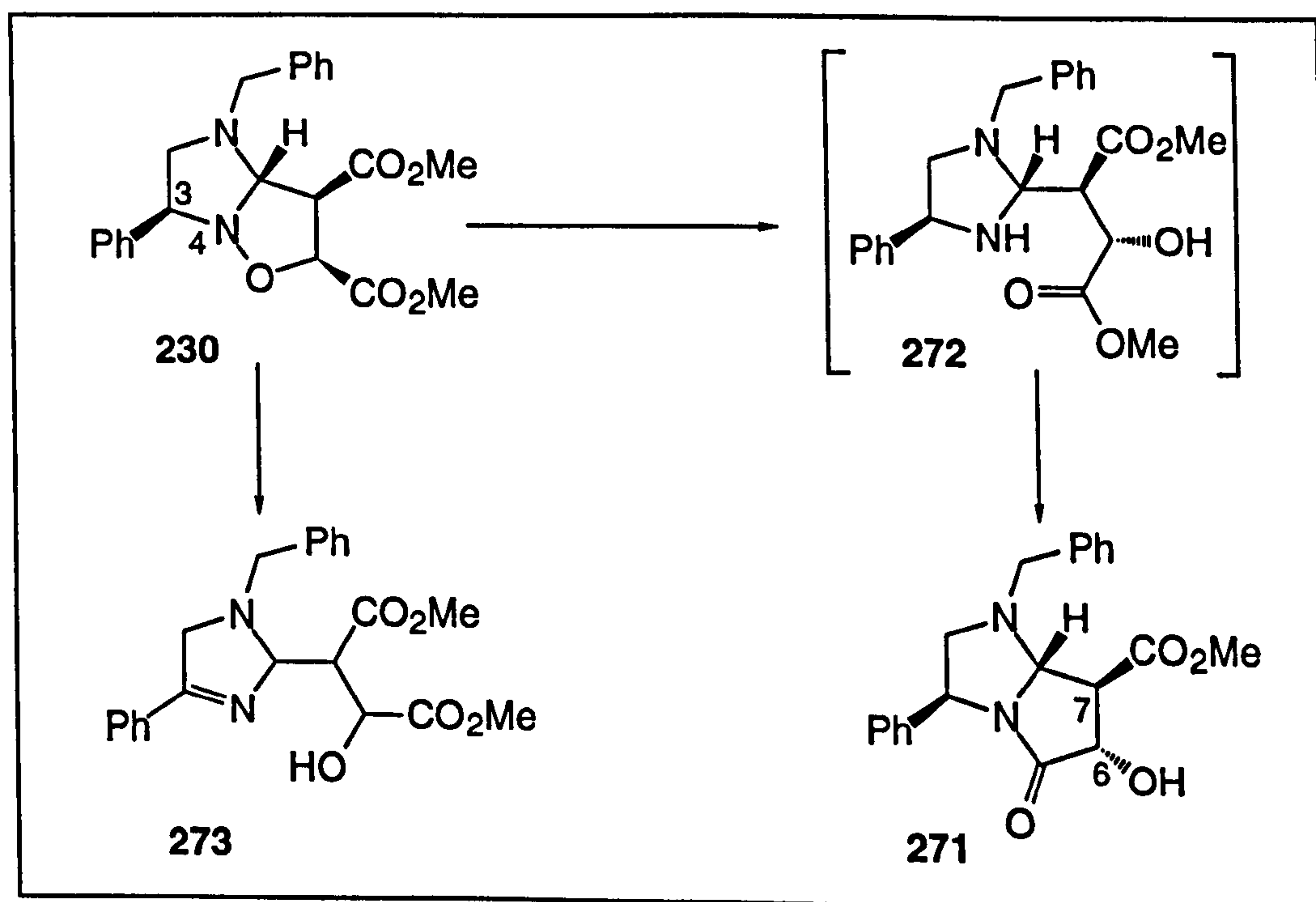


Figure 34 : X-ray crystal structure of lactam **271**.

However, assignment was not so straightforward for the relative stereochemistry of the lactam ring. We found by NOESY that the bridgehead proton H^f, and that adjacent to it, H^a showed reciprocal enhancements, suggesting that they both occupied the upper face. This suggested a total inversion of the C-7 stereochemistry of **271**, which seemed much less likely than partial epimerisation of this relatively acidic centre. We were not alarmed by this finding in the light that we had found in previous cycloadducts that this nOe was indicative of a *trans*- relationship between these two protons. We also found that irradiation of H^f enhanced H^b but not the C-6 OH whilst irradiation of the C-6 OH enhanced not only the geminal proton (H^b), but also H^a. Here, we had evidence which could assign H^f and H^b with

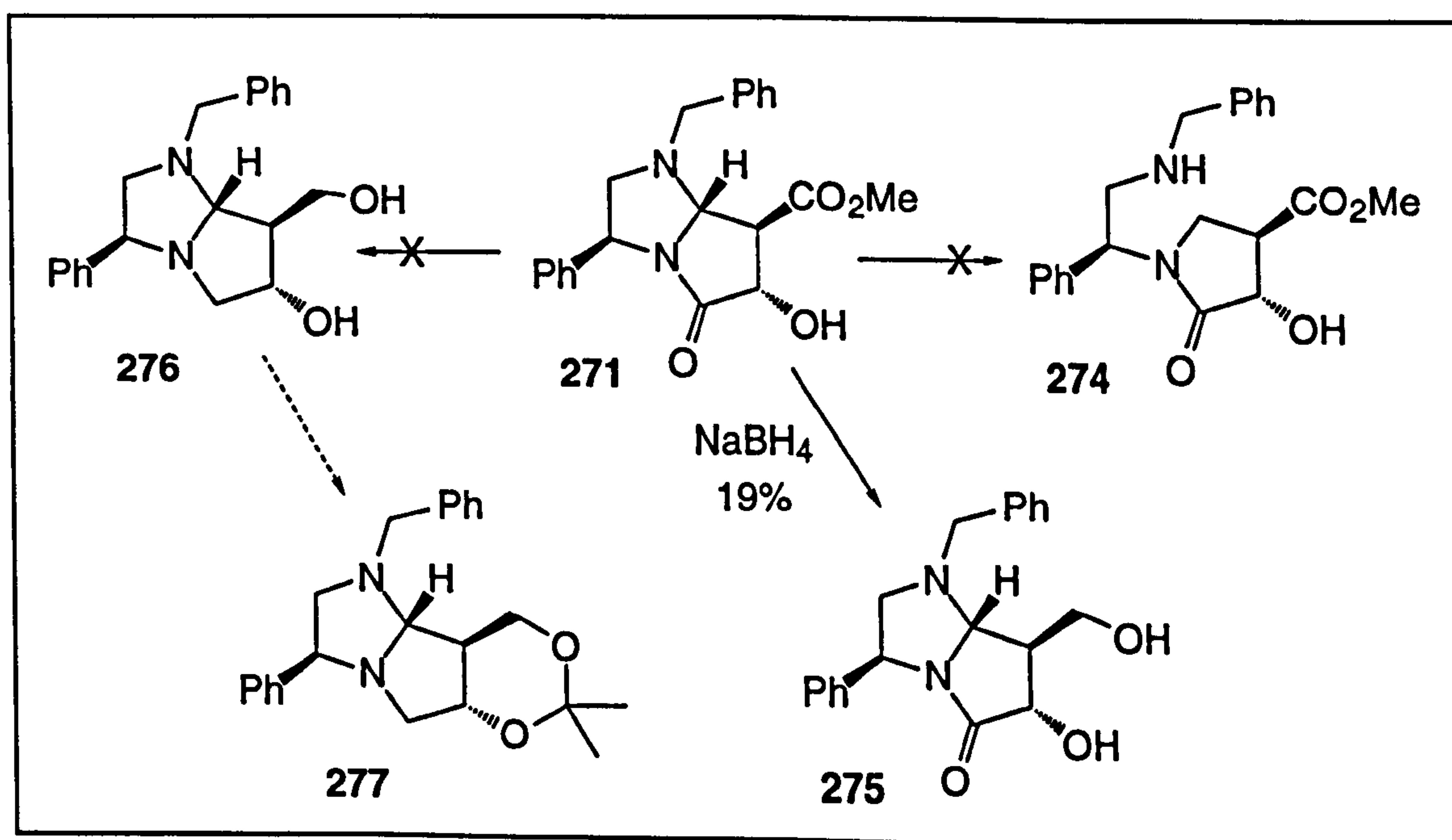
confidence to the upper face and H^a to either. Fortunately, we were able to recrystallise the lactam **271** from methanol and the resulting X-ray crystal structure (Figure 34) confirmed that the C-7 relative stereochemistry of **271** was unchanged from that of the parent cycloadduct **230** and agreed with our earlier observations that the enhancements between H^f and H^a come about through their *trans* relationship. These data support our proposed reaction pathway in which the N–O cleavage product **272** cyclises through nitrogen onto the pendant ester function (Scheme 89) to form the 5-membered lactam, rather than the strained 4-membered alternative *via* reaction with the adjacent ester function. Rotation about the carbon-carbon bond which becomes C-6 to C-7 in the pyrroloimidazolone **271** is required to bring this ester favourably close for lactamisation and so the observed stereochemistry at C-6 of this lactam will have the hydroxyl moiety below the plane of the ring as drawn whereas the ester of the parent molecule **230** was above.



Scheme 89

When the Raney nickel reduction of cycloadduct **230** was performed on a large scale, it was possible to isolate a small amount of a second product which has been identified by NMR as the 2-functionalised 3-imidazoline **273** (Scheme 89), which is formally the result of dehydrogenation across C-3 and N-4 of **230** as well as the desired N–O hydrogenolysis, but could equally arise from a proton shift from C-3 to O.

The initial N–O bond cleavage step of our template removal strategy was also applied to the cycloadducts **241** of methyl acrylate and **238** of diethyl maleate. We found that the former adduct **241** was unreactive to H₂ with 5mol% of 10% Pd-C even after 48 hours at 20°C. Atmospheric pressure hydrogenolysis with 5mol% of Pd(OH)₂, or treatment with Raney nickel at 60psi of H₂, were also unsuccessful. Similarly, the diethyl maleate cycloadduct **238** did not yield any identifiable material after elevated pressure hydrogenolysis at 20°C with Raney nickel.

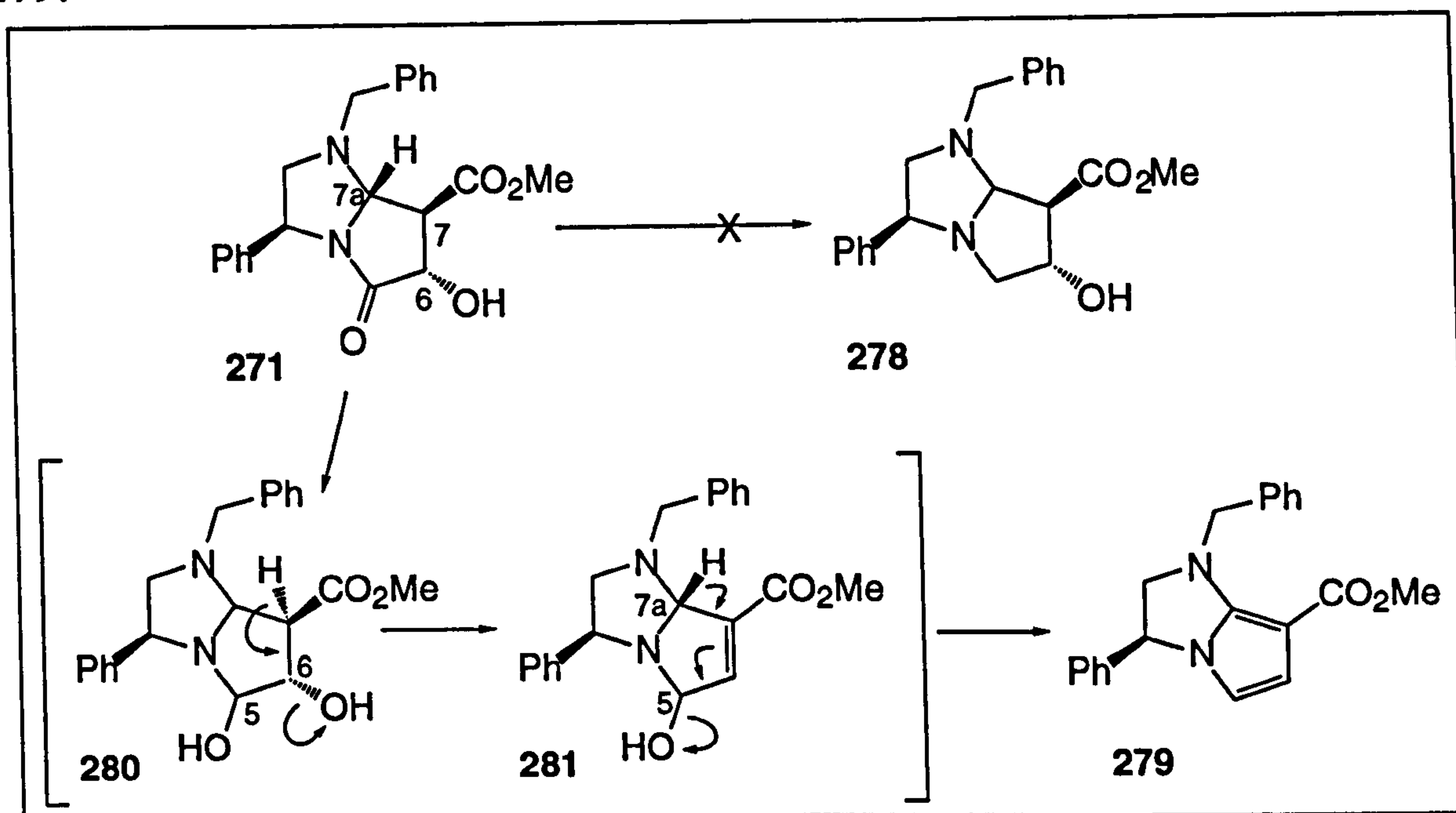


Scheme 90

Having cleaved the N–O bond, we hoped that the lactam **271** would undergo amination reduction with NaCNBH_3 to afford **274** (Scheme 90). Thus, **271** was stirred in ethanolic solution at pH 4 with NaCNBH_3 for 48 hours but without change. Reaction at room temperature with NaCNBH_3 in glacial acetic acid was unsuccessful, and heating this mixture to reflux returned an intractable mixture of products. Thus, we sought to cleave the amination with NaBH_4 , but after 72 hours at room temperature the mixture was purified by column chromatography to isolate the diol **275** (19%). This experiment was repeated in order to determine the fate of the missing material but after 18 hours at room temperature again we only isolated a 19% yield of **275**. We resolved to carry out simultaneous cleavage of the amination moiety and reduction of both the lactam and ester functionalities using LiAlH_4 , but room temperature reaction only produced complex mixtures. *In situ* trapping of the desired amino diol **276** with acetone²⁹⁴ was attempted in order to facilitate isolation of this highly polar product, if present, as the cyclic acetal **277**, but this afforded no desired material. We presume that the lone pair of the amide nitrogen of the lactam **271** is unable to participate in the amination reduction by assisting amino-iminium ion formation.

We decided to reduce the lactam carbonyl, to afford a pyrroloimidazole ring system similar to **133** (Scheme 43) for which we have a template removal strategy in hand. There is a plethora of amide reduction strategies to choose from in the literature,²⁹⁵⁻²⁹⁷ including complexed borane reagents.²⁹⁸⁻³⁰⁷ Thus, a solution of the lactam **271** in dry THF was heated at reflux with $\text{BH}_3\cdot\text{THF}$ complex for 18 hours but the isolated material was not the desired pyrroloimidazole **278** but the partially aromatic product **279** (Scheme 91). From these results, we propose that pyrrole **279** forms *via* the aminol intermediate **280** in the reduction of the lactam carbonyl. This eliminates a water molecule across the C-6 to C-7 bond taking advantage of the acidity of the C-7 proton to afford the α,β -unsaturated ester

intermediate **281**. The C-7a bridgehead proton is then lost along with the aminol C-5 hydroxyl group of **281** in a 1,4-elimination driven by aromatisation of the pyrrole ring of **279**.



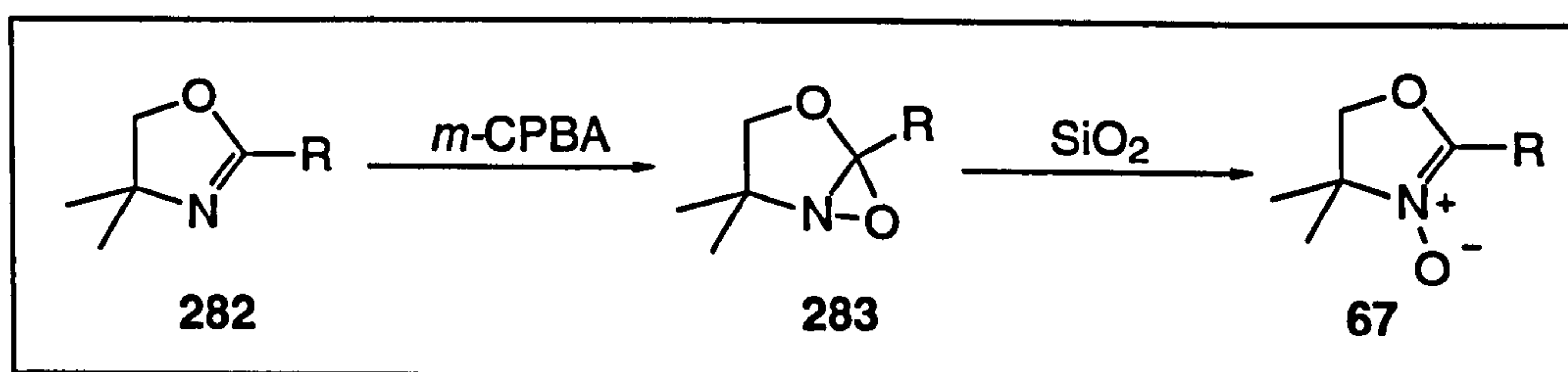
Scheme 91

Of the other known lactam reduction protocols, we attempted the trichlorosilane methodology of Nagata *et al.* who reported facile reduction of N,N-disubstituted lactams by this procedure.²⁹⁶ Thus, the lactam **271** was heated to reflux in toluene with 4 equivalents of HSiCl₃ but only the lactam starting material was isolated after 24 hours. A number of lactam reductions by catalytic hydrogenation are known,³⁰⁸ but agitation of a solution of the lactam in methanol with 5mol% of 10% Pd-C at a pressure of 60psi of H₂ did not afford the desired product, even after 72 hours.

2.5 Attempted achiral imidazoline nitron syntheses.

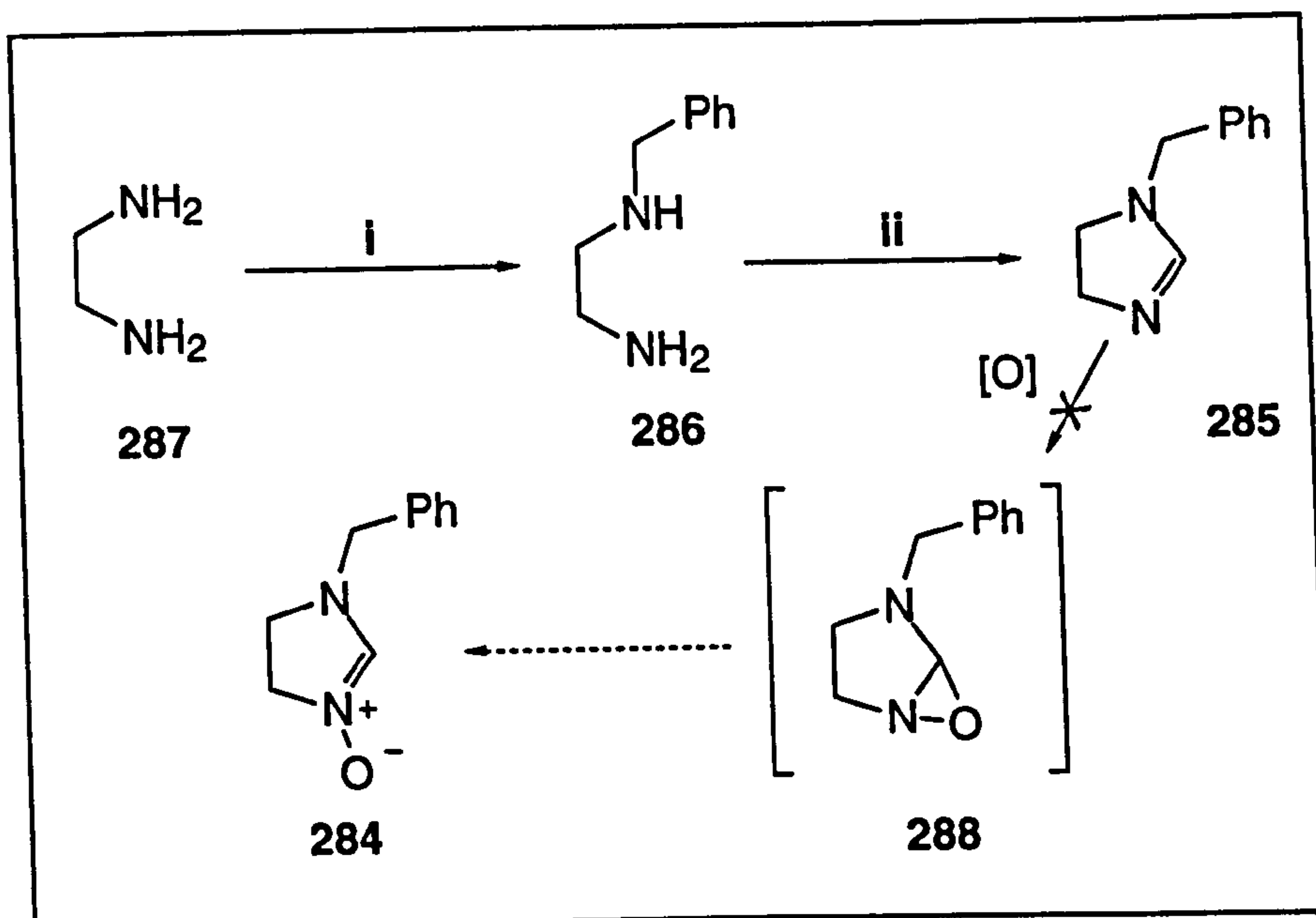
As we have described in the previous section, the development of our final synthesis of the 2-imidazoline nitrones led us a long way from the initial strategy that we proposed. We were at the same time investigating other routes to our target reagents from a diverse range of starting materials, and our findings will be reported in this section.

2.5.1 Towards nitrones *via* 2-imidazolines.



Scheme 92

It is clear from the literature that one of the mainstays of nitron preparative methods is direct oxidation of the corresponding imine.^{25,45,309} Imidazole and its derivatives are unreactive toward mild oxidation, and under more vigorous conditions yield a range of ring-cleavage products rather than the N-oxides.³¹⁰ Similarly, there is no track record of 2-imidazoline N-oxidation, although the closely analogous oxazoline nitrones have been formed in this way.^{99,311} Keana and Lee used *m*-CPBA to oxidise the oxazolines 282 to the oxaziridines 284, which spontaneously isomerised over silica gel to the moisture-sensitive nitrones 67 (Scheme 92).³¹¹



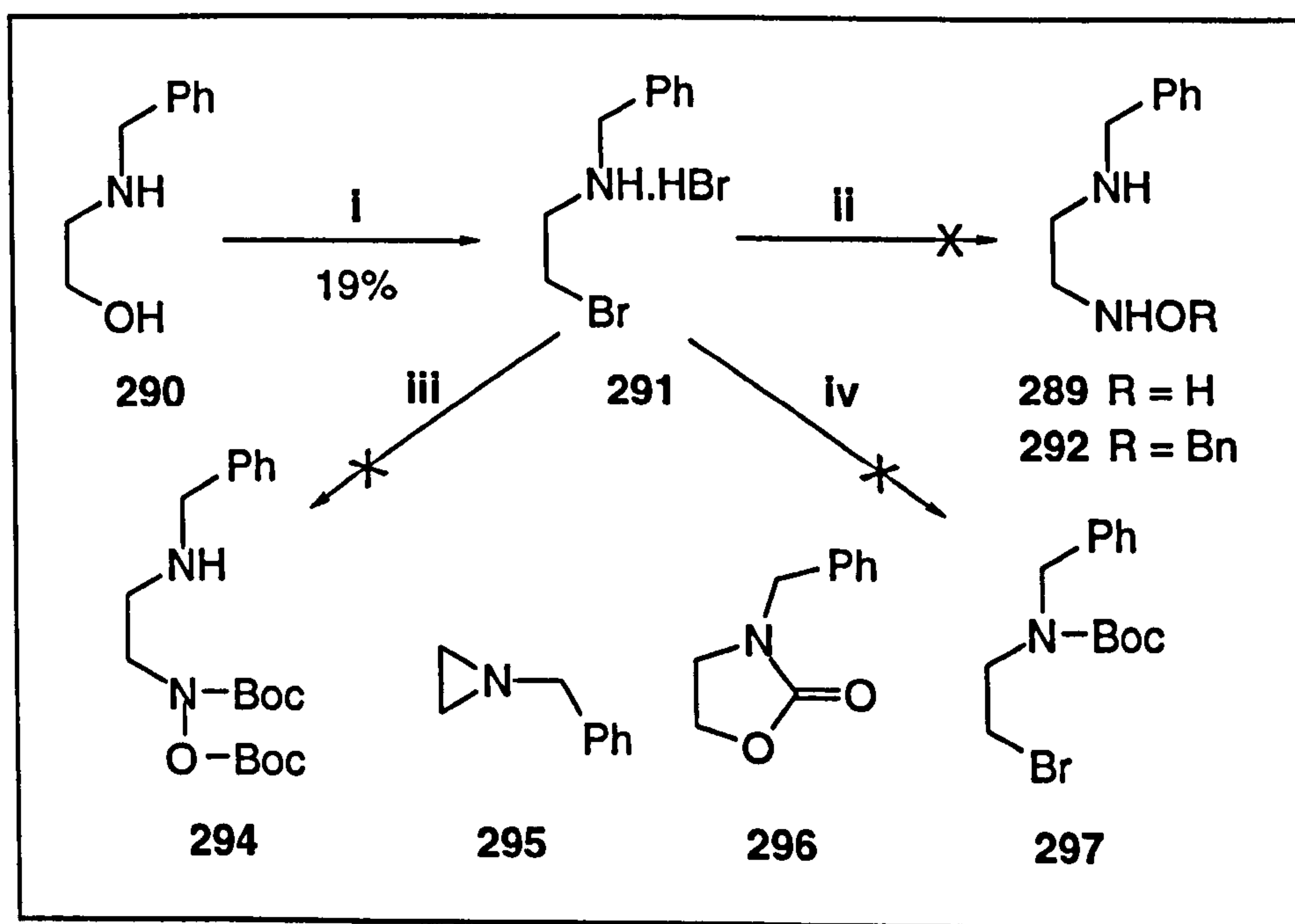
Reagents : i, BnCl, Δ, 72h; ii, HC(OEt)₃, *p*-TsOH, Δ, 36h.

Scheme 93

We proposed that we might prepare the achiral 2-imidazoline nitrone **284** by this methodology from the 2-imidazoline **285** (Scheme 93). This compound is familiar to us as the intermediate in the synthesis of the achiral 2-imidazoline azomethine ylides **125a** (Section 2.1). Therefore N-benzylethylenediamine **286** was prepared by dropwise treatment of a solution of ethylenediamine **287** with benzyl chloride at 0°C followed by 72 hours at reflux, to afford the alkylated product as a colourless oil (51%) after vacuum distillation. Cyclisation of the diamine **286** was performed with triethyl orthoformate and catalytic *p*-TsOH by heating to 130°C for 36 hours. The crude product mixture was purified by vacuum distillation to afford the 3-benzyl-4,5-dihydroimidazole **285** as a highly hygroscopic white solid (71%). Our first attempts at oxidation of **285** were performed in glacial acetic acid by heating to reflux with aqueous hydrogen peroxide. The solution was basified and extracted with chloroform to afford a mixture containing the starting material but with no indication of the nitrone **284** or the corresponding oxaziridine **288**. In an alternative oxidation procedure,

a solution of the 2-imidazoline **285** in dry ether was treated with *m*-CPBA at 0°C before warming to 20°C and stirring for 24 hours. The reaction was treated with EtOAc and 10% Na₂CO₃ before addition of solid NaCl to force the organic material from the aqueous phase. The EtOAc was dried and evaporated to afford a mixture from which only *m*-CPBA and *m*-CBA were identified. This experiment was repeated with addition at -10°C, but without success. An experiment kept at 4°C for 48 hours gave a complex mixture of products from which no nitron was could be isolated.

2.5.2 Towards nitrones from β-aminoalcohols



Reagents : i, 48% aq. HBr, 130°C, 4h; ii, NH₂OR.HCl, Et₃N, EtOH, Δ, 72h or DMF, Δ, 18h;

iii, HN(Boc)OBoc (**293**), K₂CO₃, DMF, 30°C, 18h; iv, Boc₂O, Na₂CO₃, H₂O, 20°C, 18h.

Scheme 94

The achiral nitron precursor **289** is only removed from the commercial β -amino alcohol **290** by a single functional group interconversion. However, the poor leaving group ability of the hydroxide moiety in **290** forced us to find a way to enhance its reactivity towards substitution. To this end, we proposed to prepare N-benzyl-2-bromoethylamine as its hydrobromide salt **291** by the method of Martin and Campbell,³¹² and subsequently to perform substitution of the bromide by hydroxylamine.

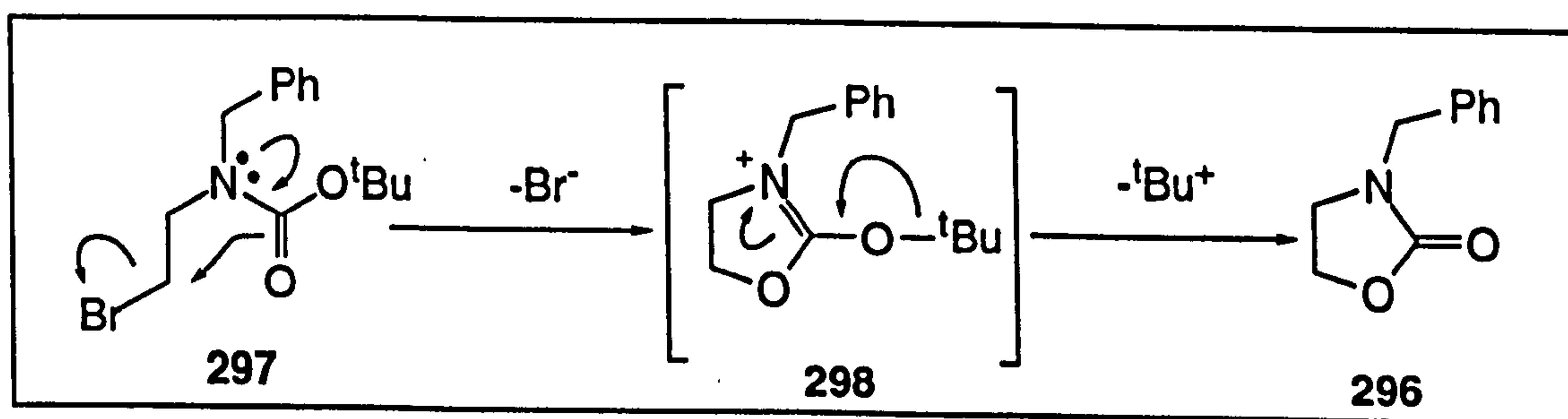
After the reaction of N-benzylethanolamine **290** and 48% aqueous HBr at 130°C for 4 hours, the brown residue was cooled and washed with ether then DCM to afford an off-white solid. This proved to contain a mixture of the desired product **291** and the starting material **290** each as their hydrobromide salt in the ratio 4:1, which corresponded to a 19% yield of the desired compound. Repeats of the procedure showed no improvement in yield or purity, which led us to attempt the substitution reaction with hydroxylamines on this mixture. Reaction with 1.1 equivalents of hydroxylamine hydrochloride or O-benzylhydroxylamine hydrochloride and 3.1 equivalents of triethylamine in ethanol yielded none of the desired substitution products **289** or **292**. Nor was success achieved with hydroxylamine after changing the solvent to THF, or with 5 equivalents of the nucleophile in ethanol. We prepared N,O-*bis-tert*-butoxycarbonylhydroxylamine **293** to use as an alternative nucleophile, from hydroxylamine hydrochloride and di-*tert*-butyl dicarbonate (Boc₂O) in aqueous sodium carbonate by the method of Whiting and Baillie³¹³ as a white crystalline solid (54%). Despite using this reagent in DMF with potassium carbonate to promote the S_N2 reaction, we isolated none of the desired product **294** after 18 hours at room temperature. A large proportion of the N,O-*bis-tert*-butoxycarbonylhydroxylamine was recovered (67%), along with the product of intramolecular nucleophilic substitution, N-

Similarly harsh conditions were applied in a synthesis of **295** with conc. sulfuric acid but only the starting material was recovered. At this point, we became aware of the aziridine preparations of Pfister using Mitsunobu chemistry.³¹⁸ He reports good yields of aziridines with substitution at one or both of the ring carbons but a poor yield of N-benzylaziridine (18%) and no reaction when the nitrogen is unsubstituted. We chose (1*R*,2*S*)-(-)-ephedrine **299** as a convenient chiral source, and treated it, in solution, with triphenylphosphine then diethyl azodicarboxylate (DEAD) before stirring at 20°C for 18 hours in an attempt to prepare the aziridine **300**. However, the only identifiable material from this reaction was the expected by-product diethoxycarbonylhydrazine. We applied these conditions to the synthesis of N-benzylaziridine **295** and N-methylaziridine **301** from the corresponding β -amino alcohols but without success. A small, impure sample of N-methylaziridine **301** was later prepared by reaction with chlorosulphonic acid and the previously described vigorous conditions.^{316,317} This material was reacted with hydroxylamine or benzylhydroxylamine (generated from the hydrochlorides *in situ* by addition of 1 equivalent of triethylamine) in the presence of catalytic ammonium chloride in methanol at room temperature for 48 hours in an attempt to prepare hydroxylamines **302a** and **302b**, but no ring-opening was observed.

At this point, we decided to re-examine the synthesis of N-benzylaziridine, this time using the mild sulfonating agent sulfur trioxide-trimethylamine complex. A mixture of N-benzylethanolamine and 1.2 equivalents of the complex were heated to reflux for 2 hours. After cooling to 60°C, the mixture was treated with excess 10M aqueous NaOH and heated at reflux for a further 2 hours. The whole mixture was cooled to room temperature and extracted with toluene, before drying and evaporation *in vacuo* to yield pure N-benzylaziridine **295** as a colourless oil (30%). This material was taken forward for ring opening with hydroxylamine but gave a highly complex mixture of products from which

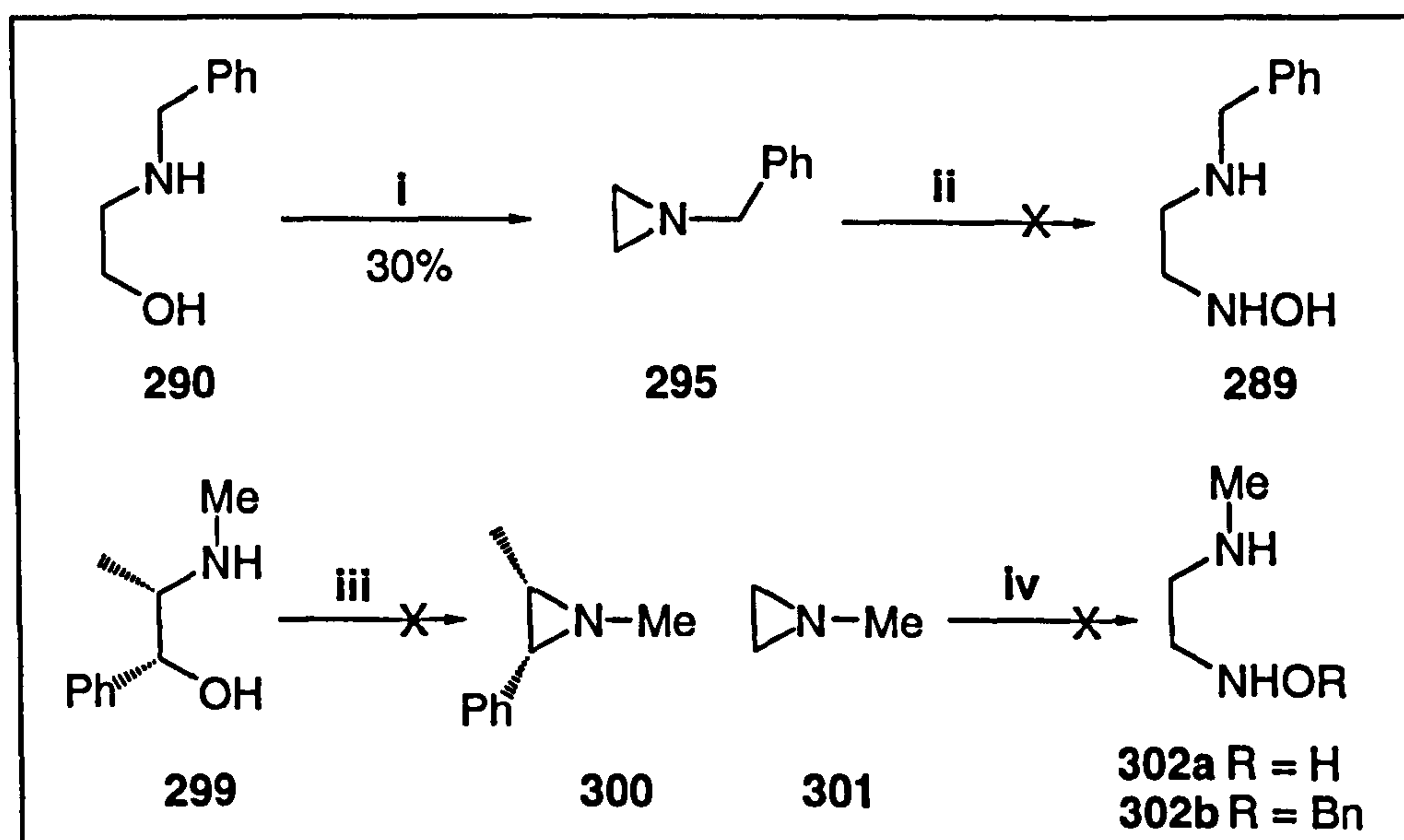
benzylaziridine **295** (42%), and the less obvious product, 3-benzyloxazolidin-2-one **296** (28%).

We attempted to deter the participation of the benzylamino moiety in the intramolecular aziridination reaction during substitution with hydroxylamines, by protection of this nucleophilic nitrogen as the carbamate. Thus, we treated a solution of the bromo amine hydrobromide **291** in aqueous sodium carbonate with Boc_2O and stirred the resulting mixture at 20°C for 48 hours. The residue yielded no desired material after column chromatography although Boc_2O (20%) was recovered, once again, along with the 3-benzyloxazolidin-2-one **296** (27%). The generation of **296** from two quite different reactions suggests a common pathway and therefore we propose that in both instances, this product is derived from the desired N-Boc bromo amine **297** (Scheme 95). In the reaction of bromo amine **291** with the *bis*-Boc-hydroxylamine **293**, we propose that the Boc-protected bromo amine **297** arises *via* transfer of the O-*tert*-butoxycarbonyl group from the *bis*-Boc reagent onto the benzylamine nitrogen. In both cases, this is then followed by attack at the α -position through donation of the benzylamino nitrogen lone pair into the N–C bond, leading to ring-closure through oxygen with the loss of bromide. Loss of the *tert*-butyl carbonium ion from intermediate **298** will regenerate the carbonyl moiety and so afford the isolated oxazolidin-2-one **296**.



Scheme 95

An alternative synthesis of achiral 2-imidazoline nitrones was devised which might afford the target compound in as little as 3 steps (Scheme 96). Firstly, we needed to prepare N-benzylaziridine **295**, available *via* any of the well-known methods for conversion of the hydroxyl moiety to a more effective nucleofuge, such as the sulfate. This would facilitate an intramolecular S_N2 reaction through the amino-nitrogen of **290** to afford the aziridine **295**. Being highly-strained ring systems, aziridines are commonly ring-opened by nucleophiles including the hydroxylamine we require to afford the desired intermediate **289**,^{314,315} the potential nitron precursor.



Reagents : i, SO₃.NMe₃, Δ, 2h then 10M aq. NaOH, Δ, 2h; ii, NH₂OH, NH₄Cl, MeOH, 30°C, 18h;

iii, Ph₃P, DEAD, Et₂O, 20°C, 18h or ClSO₃H, 130°C, 20mmHg, 2h then 16M aq. KOH; iv, NH₂OR,

NH₄Cl, MeOH, 20°C, 48h.

Scheme 96

We attempted to prepare the sulfate of N-benzylethanolamine **290** by the method of Wenker³¹⁶ and Leighton *et al.*,³¹⁷ heating to 130°C under vacuum with chlorosulfonic acid. However, after base treatment, we observed none of the desired aziridine **295**.

from the aldehyde, followed by controlled reduction to the hydroxylamine avoiding over-reduction to the amine. Our synthetic efforts were greatly assisted by methodology developed within this research group to prepare protected amino aldehydes similar to **303**. Thus, a DCM solution of commercial N-benzylglycine ethyl ester **304** was treated with Boc_2O and triethylamine and stirred at 20°C for 18 hours (Scheme 97). Thorough washing with 1M aqueous citric acid to remove excess Boc_2O , and column chromatography afforded a white solid (76%), shown to be a mixture of carbamate rotamers of protected amino ester **305** by ^1H NMR spectroscopy.

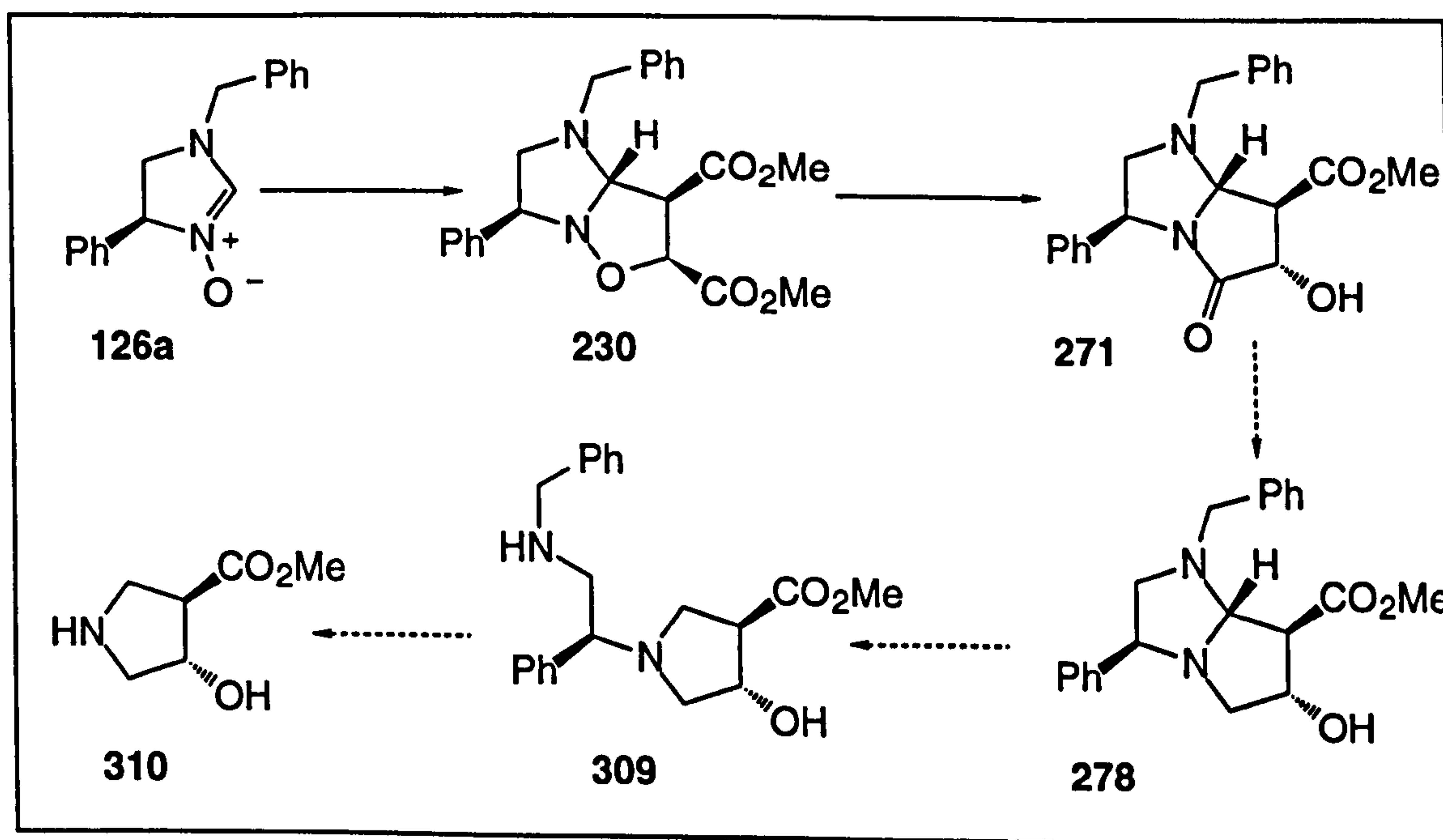
Reduction of the N-Boc-amino ester **305** was performed in dry toluene by slow addition of diisobutylaluminium hydride (DIBAL) at -78°C followed by quenching with methanol and addition of a solution of potassium sodium tartrate (Rochelle salt) to remove aluminium residues. After 1.5 hours of vigorous stirring, two phases formed from which the organic phase was separated to afford the N-Boc-amino aldehyde **303** as a colourless oil (82%). Once again, the product was shown to exist as a mixture of carbamate rotamers by ^1H NMR spectroscopy. This aldehyde was treated with a solution of sodium acetate and hydroxylamine hydrochloride to form 2 immiscible phases which were not combined by addition of a little ethanol. Despite this, the mixture was heated to 60°C for 2 hours before cooling to 20°C and, after column chromatography, afforded the β -oximino amine **306** as a white solid (48%).

$\text{BH}_3\cdot\text{THF}$ complex is one of the few reducing agents capable of performing the controlled reduction of an oxime to a hydroxylamine without over-reduction to the amine. Therefore, a solution of the oxime in dry THF was treated with $\text{BH}_3\cdot\text{THF}$ at 20°C dropwise under an atmosphere of nitrogen. After 60 hours at 20°C , the solution was treated with 6M aqueous HCl and stirred for 1 hour, before basifying with KOH and extraction into DCM.

However, the desired hydroxylamine **289** was not isolated from the intractable mixture so formed. It is reported in the literature that O-acetylation enhances the reactivity of an oxime towards reduction.²²⁴ To this end, a solution of the oximino amine **306** in pyridine was treated with acetyl chloride at 0°C before stirring at 20°C for 18 hours.³¹⁹ The solution was then partitioned between ether and aqueous citric acid, but none of the desired O-acetyloxime **307** was isolated after column chromatography. The aldehyde **303** was also used in an experiment to prepare the O-benzyloximino amine **308** but, again, none of the desired oxime was observed.

2.6 Future work

We have demonstrated that the 2-imidazoline nitron 126a shows complete diastereofacial selectivity in its 1,3-dipolar cycloaddition reactions. Thus, in future work, this methodology will be applied to *homochiral* nitrones (*R*)- and (*S*)-126a, potentially available *via* one of the strategies outlined in Section 2.2.3. Once a method for reduction of the lactam 271 is found, it will be possible to apply the developed template removal methodology. Here, amination cleavage of 278 by sodium cyanoborohydride would afford the N-substituted pyrrolidine 309. Debenzylation of 309 by catalytic hydrogenolysis would then furnish 310 and complete the route to homochiral functionalised pyrrolidines *via* nitron cycloadditions (Scheme 97).



Scheme 97

Chapter 3

Experimental

Instrumentation

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a JEOL JNM-EX400 (400MHz and 100MHz respectively) or a JNM-LA300 (300Mz and 75MHz respectively) Fourier Transform NMR spectrometer. Chemical shift values are reported in parts per million (ppm) from tetramethylsilane (TMS) or 3-(trimethylsilyl)-2,2,3,3-tetradeuteropropionic acid sodium salt (TSP- d_4) as the internal standard for ^1H spectra, and from the solvent peaks for ^{13}C spectra. Multiplicities are given as s-singlet, d-doublet, q-quartet, m-multiplet and br-broad signal. Coupling constants (J) are expressed in Hz to one decimal place. Infrared spectra were recorded using a Perkin-Elmer 1710 Fourier Transform Infrared spectrometer. Optical rotation measurements were made using a JASCO DIP-1000 digital polarimeter. Low resolution mass spectra were recorded on a VG Micromass VG-250 mass spectrometer by electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) in a thioglycerol matrix in both positive and negative ion modes. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry Service (University of Wales, Swansea). Elemental analyses were performed by MEDAC Ltd. and X-ray crystallography by the EPSRC X-Ray Crystallographic Service (University of Southampton). Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. APCI was performed on a Fisons VG Platform instrument from samples in methanol or acetonitrile solution.

All column chromatography was carried out using Fluka Silica Gel 60 (220-440mesh) (Brockmann 2-3). TLC analysis was carried out using Machery-Nagel Polygram SIL G/UV₂₅₄ plates on a plastic backing (with fluorescent indicator) and visualised by ultraviolet light or aqueous potassium permanganate spray ($\text{KMnO}_4:\text{K}_2\text{CO}_3:\text{water}$, 6:1:100,

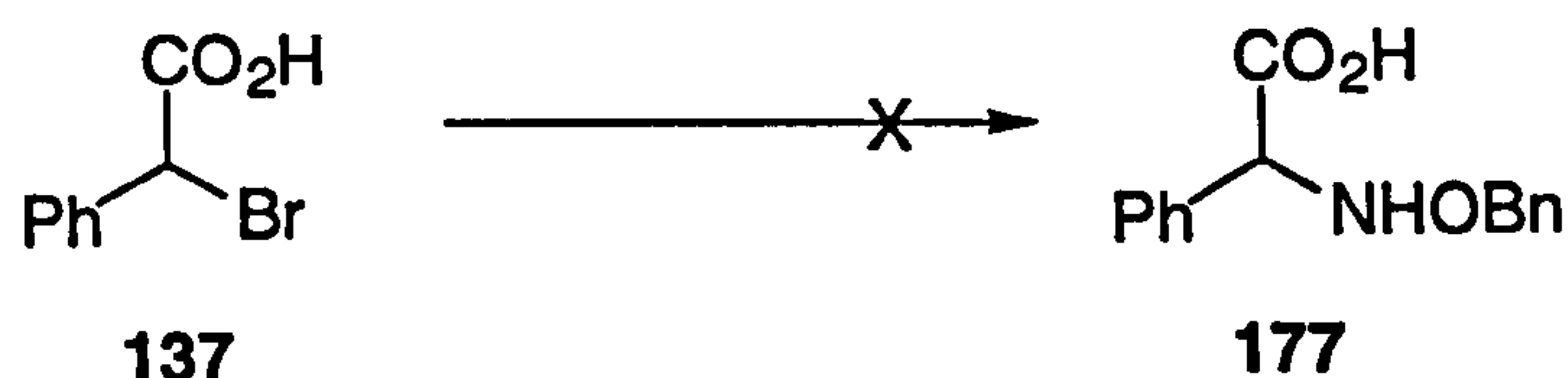
w/w/v). All chemicals were purified by distillation or recrystallisation where appropriate. THF, toluene and ether were dried over sodium or potassium and distilled. DCM was dried over sodium hydride and distilled. Dry reactions were carried out using oven-dried glassware with all transfers performed using oven-dried syringes and syringe needles.

2-Bromo-2-phenylacetic acid (137)



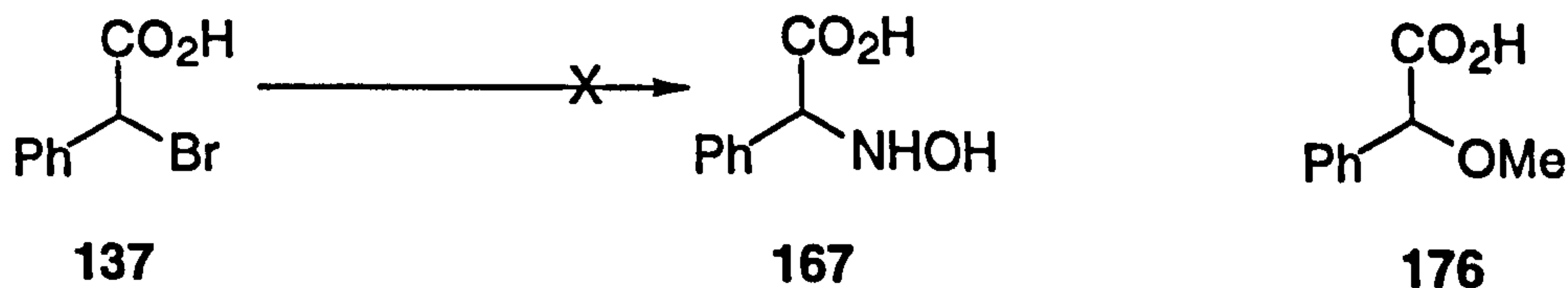
A solution of 2-phenylglycine **127** (0.500g, 3.31mmol) in aqueous HBr (48% w/v; 4cm³) was treated with a solution of sodium nitrite (0.250g, 3.64mmol) in water (2cm³) at 0°C. After stirring for 30 min, the mixture was warmed to 20°C and stirred for a further hour. The mixture was diluted with water (10cm³) and extracted with DCM (3 x 50cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound **137** as a cream-coloured solid (0.340g, 48%), mp 79-80°C (lit.,³²⁰ 81-84°C); ν_{\max} (KBr) /cm⁻¹ 3400-2500, 1715, 1457, 1418, 1291, 1233, 1167, 1148, 917, 719, 701; δ_{H} (CDCl₃; 400MHz) 5.35 (s, 1H, PhCHBr), 7.36 & 7.55 (m, 5H, Ar-H), 10.08 (br s, 1H, CO₂H); δ_{C} (CDCl₃; 100MHz) 46.1 (PhCHBr), 128.7, 128.9 & 129.6 (Ar-CH), 134.9 (Ar-C), 174.0 (CO₂H); m/z 214 (M⁺-H, 7%), 171 (11%), 169 (11%), 136 (12%), 135 (100%), 118 (5%), 107 (34%), 90 (32%).

Attempted preparation of 2-benzyloxyamino-2-phenylacetic acid (177)



To a solution of 2-bromo-2-phenylacetic acid **137** (0.100g, 0.465mmol) in DCM (5cm³) was added dropwise a solution of triethylamine (0.280cm³, 2.01mmol) and O-benzylhydroxylamine hydrochloride (80.0mg, 0.501mmol) in DCM (5cm³). The solution was heated to reflux for 18 h and, after cooling to 20°C, acidified with aqueous HCl (2M; 30cm³) and extracted with DCM (3 x 50cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated but the residue yielded none of the desired material after column chromatography (SiO₂, hexane:EtOAc 1:1 v/v).

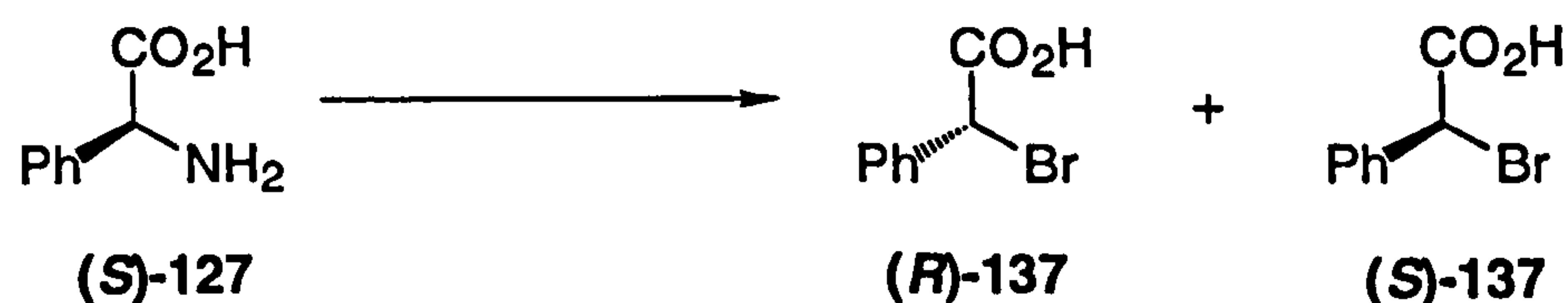
Attempted preparation of 2-hydroxyamino-2-phenylacetic acid (167)



To a solution of sodium (0.920g, 40.0mmol) in anhydrous methanol (15cm³) was added hydroxylamine hydrochloride (1.16g, 16.7mmol). To this solution was added **137** (2.00g, 9.30mmol) before heating to reflux for 18 h. The solution was acidified with aqueous HCl (2M) and extracted with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated and the residue purified by column

chromatography (SiO₂, DCM:MeOH 19:1 v/v) to afford 2-methoxy-2-phenylacetic acid **176** (0.21g, 21%) as a brown oil; δ_{H} (CDCl₃; 400MHz) 3.40 (s, 3H, OCH₃), 4.79 (s, 1H, PhCH), 7.26-7.49 (m, 5H, Ar-H), 9.01 (br s, 1H, CO₂H); δ_{C} (CDCl₃; 100MHz) 57.3 (OCH₃), 82.0 (PhCH), 127.2, 128.6 & 129.0 (Ar-CH), 135.3 (Ar-C), 175.4 (C=O).

Attempted preparation of (*R*)-2-bromo-2-phenylacetic acid ((*R*)-137**)**



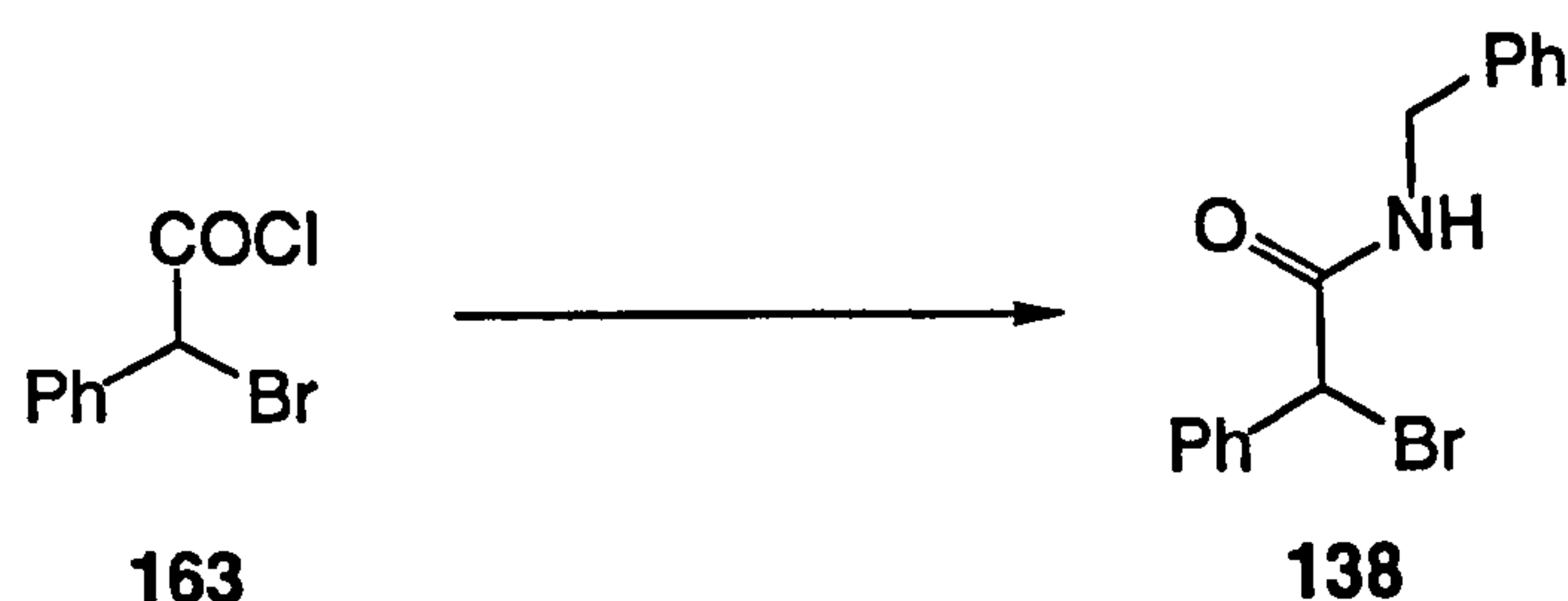
A solution of (*S*)-(+)-2-phenylglycine (*S*)-**127** (5.00g, 33.1mmol) in water (15cm³) and aqueous HBr (48% w/v; 10cm³) was treated with a solution of sodium nitrite (2.50g, 36.4mmol) in water (5cm³) dropwise at 0°C over 30 min. After warming to 20°C overnight, the solution was extracted with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered then evaporated under reduced pressure and purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford a cream-coloured solid whose data was consistent with **137** (1.71g, 24%) prepared earlier in racemic form. Optical rotation measurement showed almost total racemisation: $[\alpha]_{\text{D}}^{20} = 0.73^\circ$, DCM; $c = 0.15$ (lit.,²⁰⁰ - 178°, benzene, $c = 2$ for *R*-enantiomer).

2-Bromo-2-phenylacetyl chloride (163)



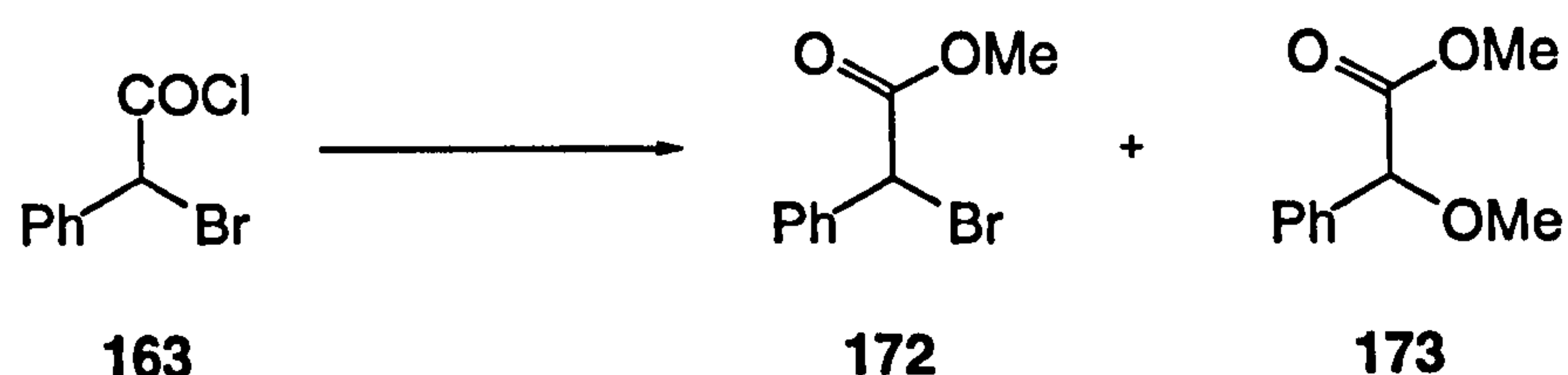
A solution of 2-bromo-2-phenylacetic acid **127** (10.0g, 64.5mmol) in DCM (30cm³) was treated dropwise with thionyl chloride (3.73cm³, 51.2mmol) and heated to reflux for 24 h, protected from the atmosphere by a calcium chloride guard tube. Evaporation of the solvent under reduced pressure gave a brown oil which was distilled under reduced pressure to afford the title compound **163** as a yellow oil (9.90g, 91%), bp 142-148°C at 20mmHg, (lit.,³²¹ 135-137°C at 20mmHg); ν_{\max} (film) /cm⁻¹ 3066, 3034, 1801, 1494, 1456, 1005, 981, 916, 697; δ_{H} (CDCl₃; 400MHz) 5.67 (s, 1H, PhCHBr), 7.40-7.49 (m, 5H, Ar-H); δ_{C} (CDCl₃; 100MHz) 54.8 (PhCHBr), 128.9, 129.4 & 130.2 (Ar-CH), 133.4 (Ar-C), 167.9 (C=O); m/z 234 (MH⁺, 16%), 199 (2%), 172 (8%), 171 (94%), 169 (95%), 163 (12%), 153 (31%), 127 (28%), 125 (100%), 91 (17%), 90 (94%).

2-Bromo-2-phenyl-N-benzylacetamide (138)



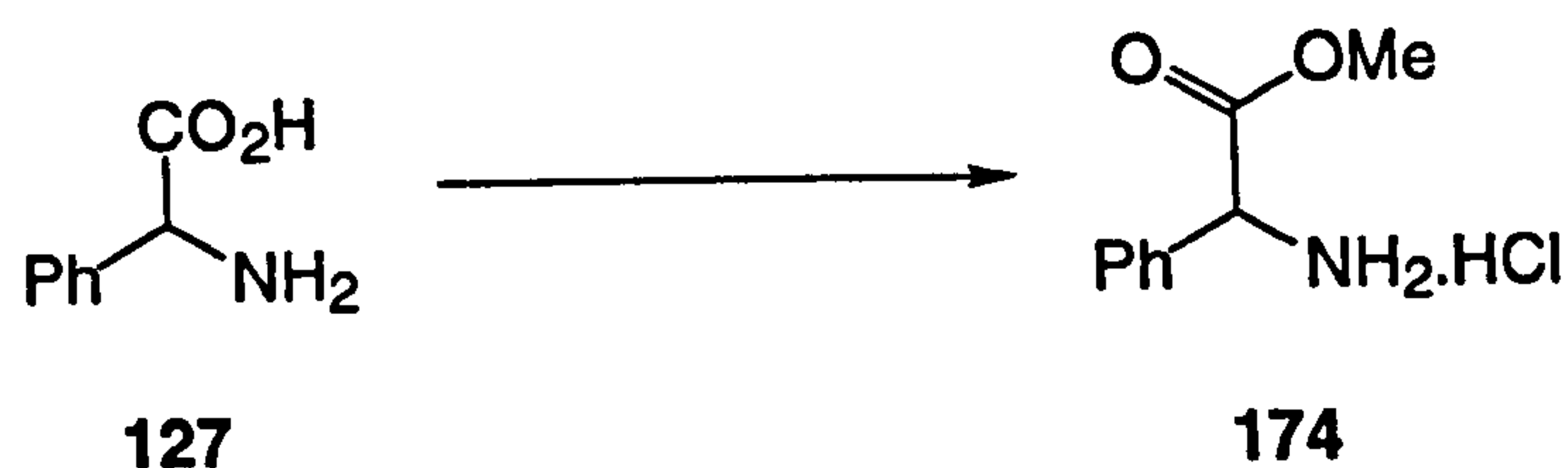
To a stirred solution of benzylamine (8.83cm³, 80.9mmol) in ether (250cm³) at 0°C was added 2-bromo-2-phenylacetyl chloride **163** (9.00g, 38.5mmol) in ether (50cm³). A thick, white precipitate formed instantly on addition, which was collected by filtration under reduced pressure and washed with ether (50cm³) and aqueous HCl (2M; 50cm³) before drying under reduced pressure to give the title compound **138** as an off-white solid (9.45g, 31.1mmol, 81%), mp 94-95°C (lit.,³²² 96-97°C); ν_{\max} (nujol) /cm⁻¹ 3289, 2923, 2854, 1660, 1480; δ_{H} (CDCl₃; 400MHz) 4.46 (m, 2H, NHCH₂Ph), 5.45 (s, 1H, PhCHBr), 7.03 (br s, 1H, NH), 7.24-7.45 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 44.3 (NHCH₂Ph), 51.3 (PhCHBr), 127.7, 128.3, 128.8, 128.9 & 129.1 (Ar-CH), 137.3 & 137.4 (Ar-C), 167.1 (C=O); m/z 304 (M⁺, <1%), 224 (95%), 196 (9%), 181 (48%), 169 (35%), 118 (40%), 106 (53%), 91 (100%).

Methyl 2-bromo-2-phenylacetate (172)



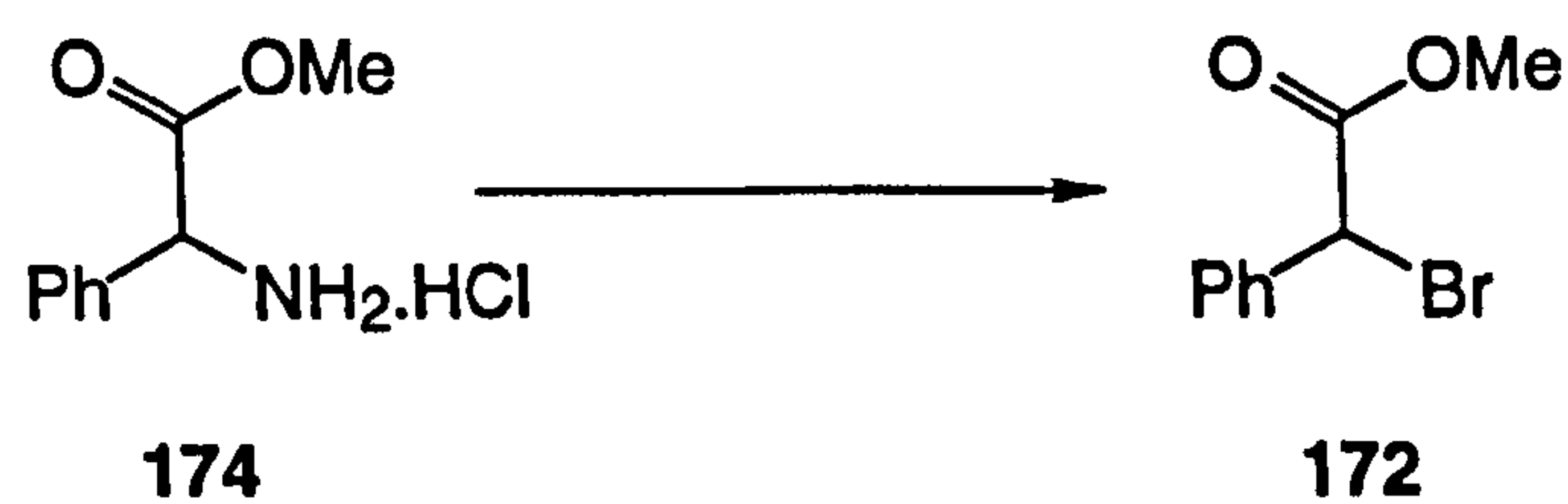
A solution of 2-bromo-2-phenylacetyl chloride **163** (1.80g, 7.71mmol) in methanol (50cm³) was heated to reflux for 18 h, protected from the atmosphere by a calcium chloride guard-tube. Evaporation of the solvent gave a pale brown, mobile oil which, after column chromatography (SiO₂, hexane:EtOAc 4:1 v/v), gave the title compound **172** material as a colourless oil (0.620g, 35%); δ_{H} (CDCl₃; 400MHz) 3.77 (s, 3H, OCH₃), 5.36 (s, 1H, PhCHBr), 7.36 & 7.52 (m, 5H, Ar-H);³²³ δ_{C} (CDCl₃; 100MHz) 46.5 (OCH₃), 53.4 (PhCHBr), 128.6, 128.8 & 129.3 (Ar-CH), 135.7 (Ar-C), 168.7 (C=O) ; m/z 228 (M-H⁺, 2%), 184 (29%), 169 (13%), 149 (66%), 125 (100%), 121 (39%), 105 (24%), 89 (44%). Also isolated by chromatography was a trace of methyl 2-methoxy-2-phenylacetate **173**; δ_{H} (CDCl₃; 400MHz) 3.40 (s, 3H, PhCHOCH₃), 3.71, (s, 3H, CO₂CH₃), 4.78 (s, 1H, PhCH), 7.33-7.45 (m, 5H, Ar-H).

Phenylglycine methyl ester hydrochloride (174)



A solution of phenylglycine **127** (1.00g, 6.62mmol) in methanol (30cm³) was treated with thionyl chloride (0.530cm³, 7.28mmol) at 0°C. The solution was heated to reflux for 3 h before evaporation of the solvent under reduced pressure to afford **174** as a white solid (1.29g, 97%), mp 196-197°C (lit.,³²⁴ 205-207°C); δ_{H} (d₆-DMSO; 400MHz) 3.72 (s, 3H, CO₂CH₃), 5.24 (s, 1H, PhCHNH₃⁺), 7.43-7.58 (m, 5H, Ar-H), 9.28 (br s, 3H, NH₃⁺);³²⁵ δ_{C} (CDCl₃; 100MHz) 53.0 & 55.2 (CO₂CH₃ & PhCHNH₃⁺), 128.2, 128.8 & 129.4 (Ar-CH), 132.5 (Ar-C), 168.7 (C=O).

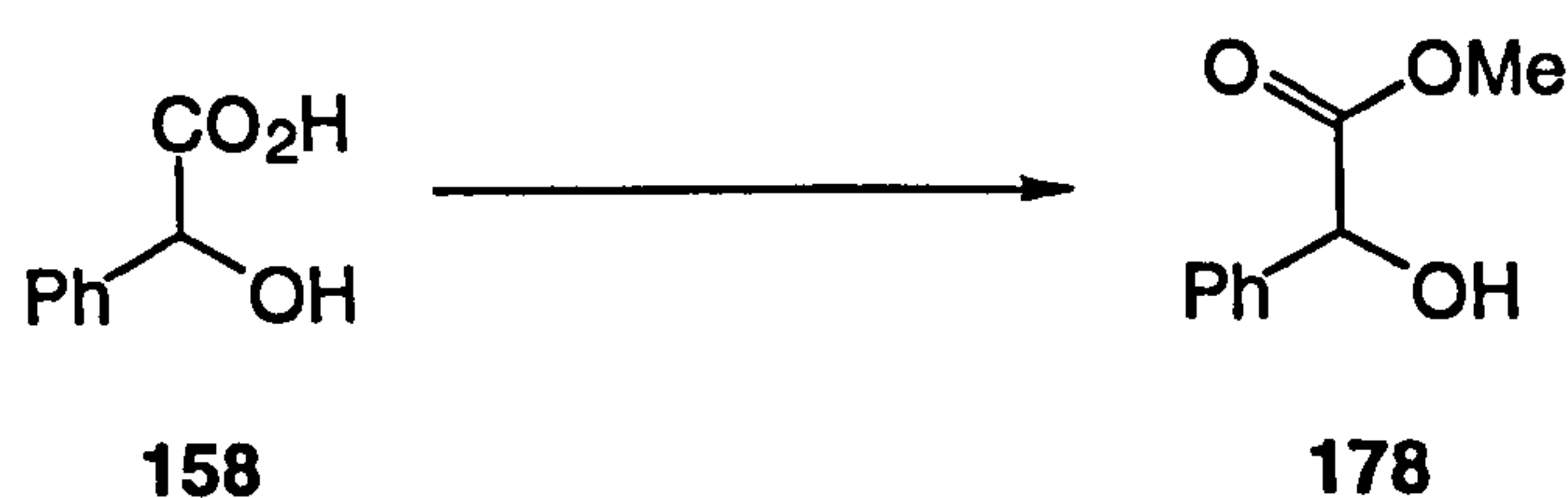
Methyl 2-bromo-2-phenylacetate (172)



A solution of phenylglycine methyl ester hydrochloride **174** (1.00g, 6.62mmol) in water (3cm³) and aqueous HBr (48% w/v; 4cm³) was treated with a solution of sodium nitrite (0.500g, 7.25mmol) in water (1cm³) at 0°C with stirring in one portion. After 30 min at 0°C, the reaction was allowed to warm to 20°C overnight. The reaction was diluted with

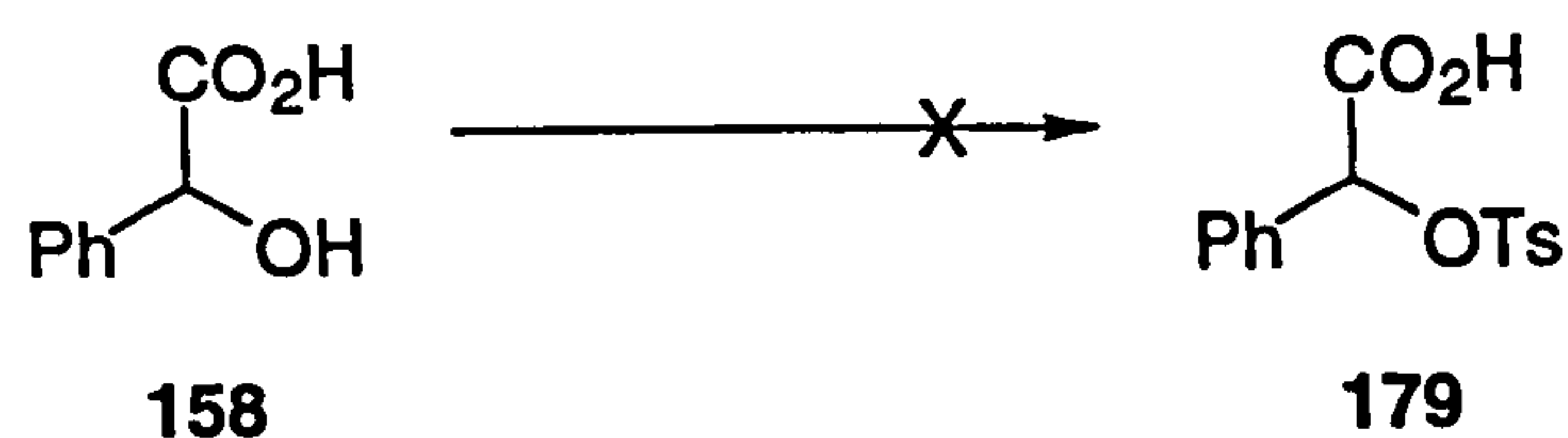
water (10cm³) and extracted with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford **172** as a brown oil (40.0mg, 4%), having data identical to a sample described above.

Methyl mandelate (**178**)



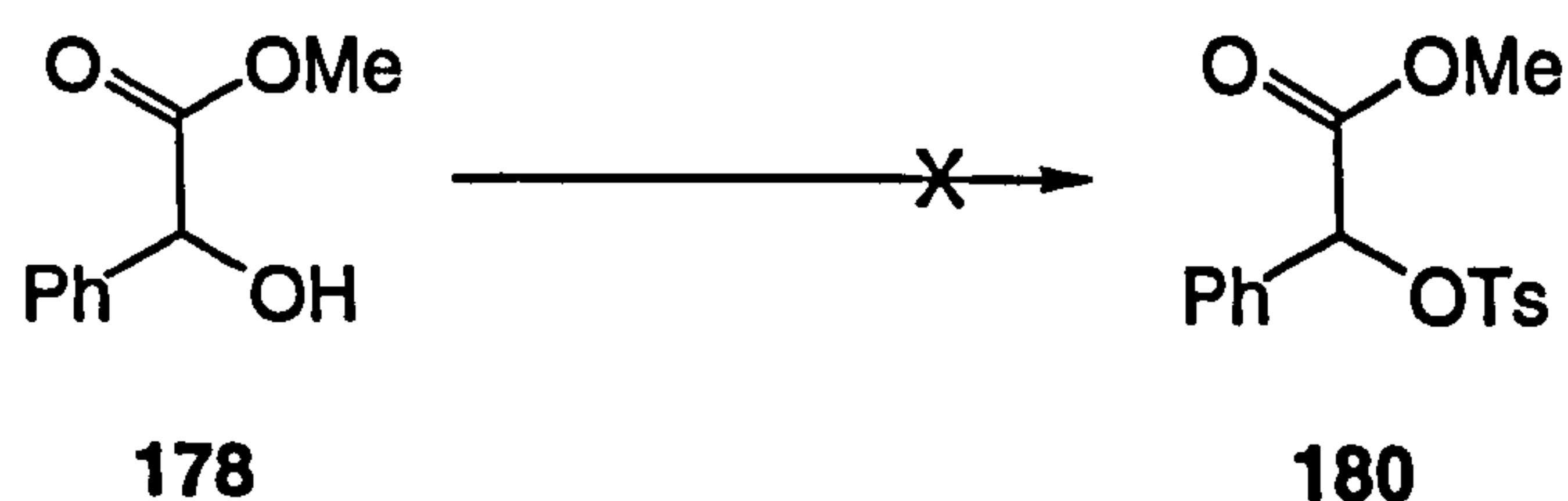
A solution of *l*-mandelic acid **158** (5.00g, 32.9mmol) in methanol (150cm³) at 0°C was treated dropwise with thionyl chloride (2.64cm³, 36.1mmol). The solution was heated under reflux for 18 h before evaporation of the solvent under reduced pressure. The brown, crystalline residue was taken up in CHCl₃ (150cm³) and the solution washed with aqueous NaOH (2M; 3 x 150cm³), before drying (MgSO₄), filtering and evaporation to dryness to afford the title compound **178** as an off-white crystalline solid (4.40g, 81%); δ_{H} (d₆-DMSO; 400MHz) 3.58 (br s, 1H, OH), 3.71 (s, 3H, OCH₃), 5.16 (s, 1H, PhCHOH), 7.30-7.41 (m, 5H, Ar-H); δ_{C} (d₆-DMSO; 100MHz) 51.6 (OCH₃), 55.2 (PhCHOH), 126.4, 127.7 & 128.0 (Ar-CH), 139.3 (Ar-C), 172.8 (C=O).

Attempted preparation of 2-(*p*-toluenesulfonyl)mandelic acid (179)



A stirred solution of *l*-mandelic acid **158** (1.00g, 6.57mmol) in acetonitrile (30cm³) at 20°C was treated with triethylamine (1.97cm³, 14.1mmol). The solution was cooled to 0°C and treated with a solution of *p*-toluenesulfonyl chloride (2.63g, 13.8mmol) in acetonitrile (30cm³) dropwise and stirred at 0°C for 30 min. TLC analysis showed no sign of reaction, and so the solution was warmed to 20°C for 1 h but without observable change. After heating the solution at reflux (80°C) for 18 h, the solvent was removed under reduced pressure but the residue did not contain any of the desired material **179**.

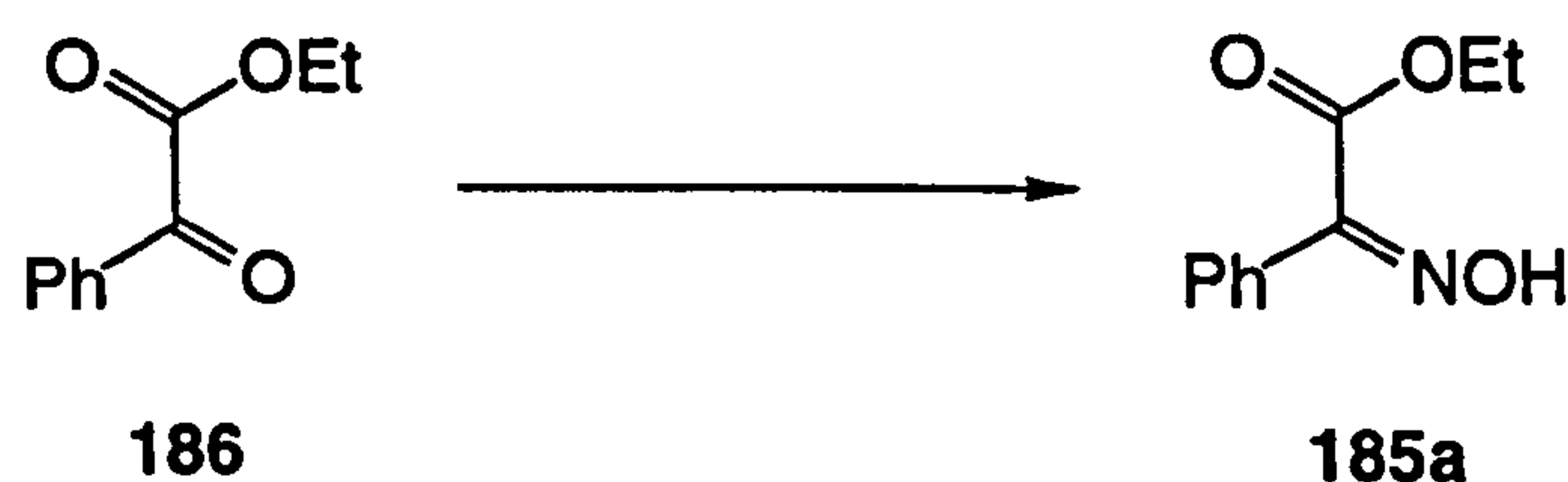
Attempted preparation of methyl 2-(*p*-toluenesulfonyl)mandelate (180)



Using the procedure described for the attempted preparation of 2-(*p*-toluenesulfonato)mandelic acid **179**, a solution of methyl mandelate **178** (0.100g, 0.602mmol) in chloroform (5cm³) was treated with triethylamine (0.170cm³, 1.20mmol) then *p*-tosyl chloride (0.130g, 0.661mmol). An identical procedure used pyridine (97.0μl,

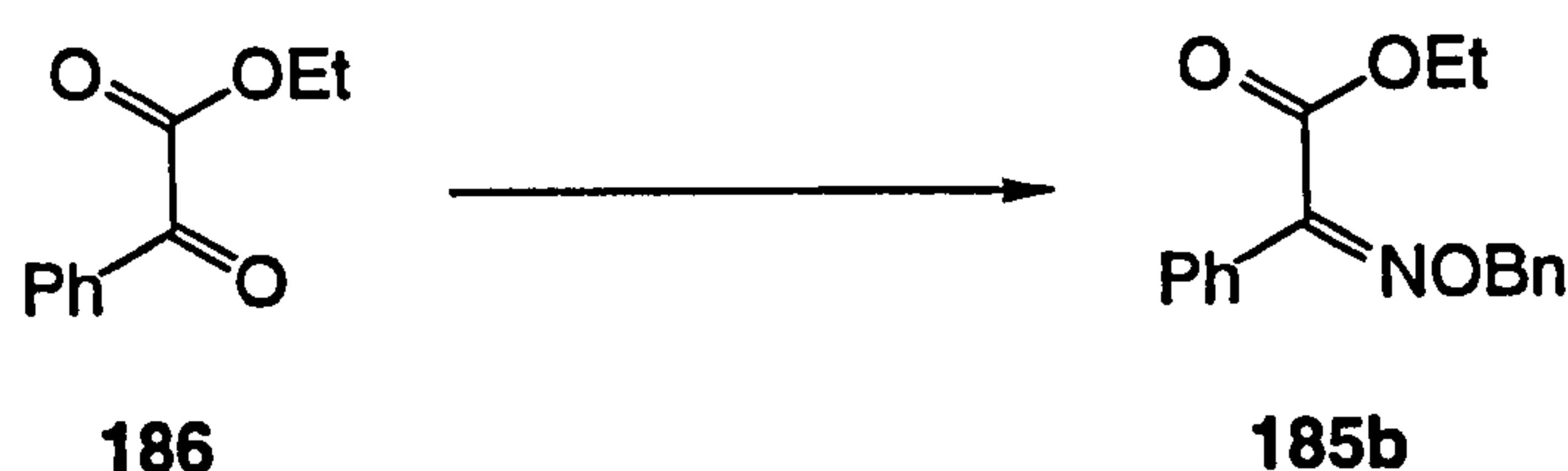
1.20mmol) and acetonitrile (5cm³). In both cases the crude reaction mixture was purified by column chromatography (SiO₂, EtOAc:hexane 1:1 v/v), but afforded only starting material **178** and an intractable mixture of products.

Ethyl 2-phenyl-2-hydroxyiminoacetate (**185a**)



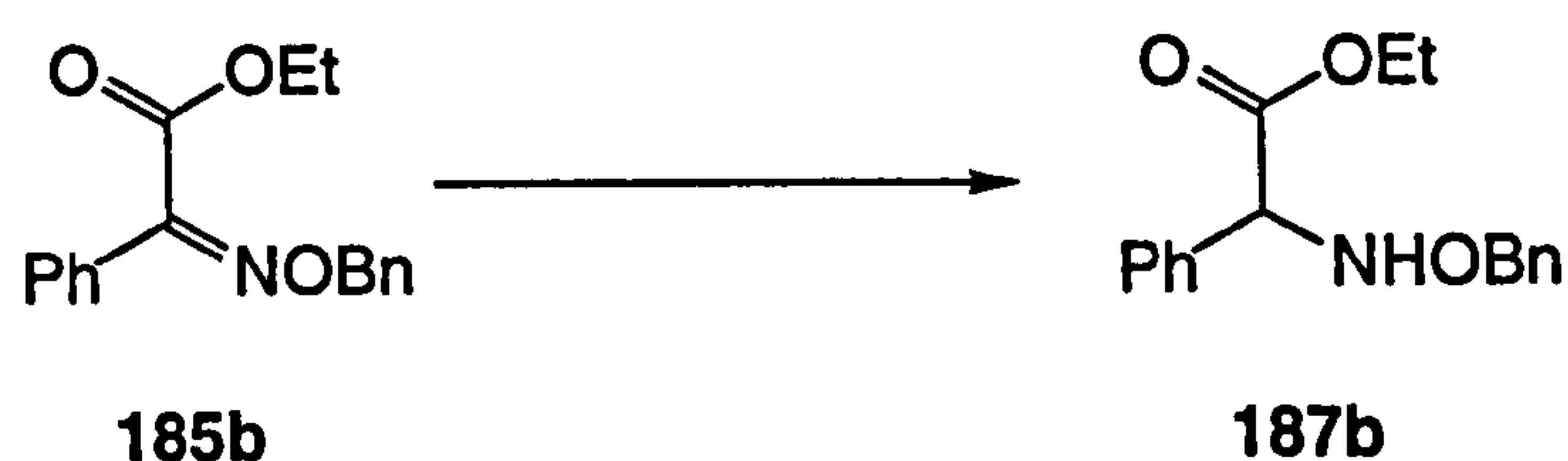
A solution of ethyl benzoylformate **186** (2.00g, 11.2mmol), hydroxylamine hydrochloride (0.86g, 12.3mmol) and pyridine (0.996cm³, 12.3mmol) in absolute ethanol (20cm³) was heated under reflux for 1 h. The solvent was evaporated and the residue purified by column chromatography (SiO₂, hexane: EtOAc 4:1 v/v) to yield the title compound **185a** as a clear oil which slowly crystallised on standing to a white crystalline solid (0.690g, 32%); ν_{max} (film) /cm⁻¹ 3409, 1737, 1499, 1448, 1372, 1308, 1219, 1042, 1025, 1001, 944, 770, 691, 666, 655; δ_{H} (CDCl₃; 400MHz) 1.42 (t, 3H, OCH₂CH₃, *J* 7.2Hz), 4.47 (q, 2H, OCH₂CH₃, *J* 7.2Hz), 7.38 & 7.58 (m, 5H, Ar-H), 8.83 (br s, 1H, NOH); δ_{C} (CDCl₃; 100MHz) 14.1 (OCH₂CH₃), 62.1 (OCH₂CH₃), 126.4, 128.8, 130.2 & 130.5 (Ar-C & Ar-CH), 151.9 (PhC=NOH), 163.6 (CO₂Et); *m/z* 193 (M⁺, 52%), 164 (5%), 147 (29%), 120 (60%), 119 (69%), 104 (38%), 103 (42%), 77 (100%).

Ethyl 2-phenyl-2-benzyloxyiminoacetate (185b)



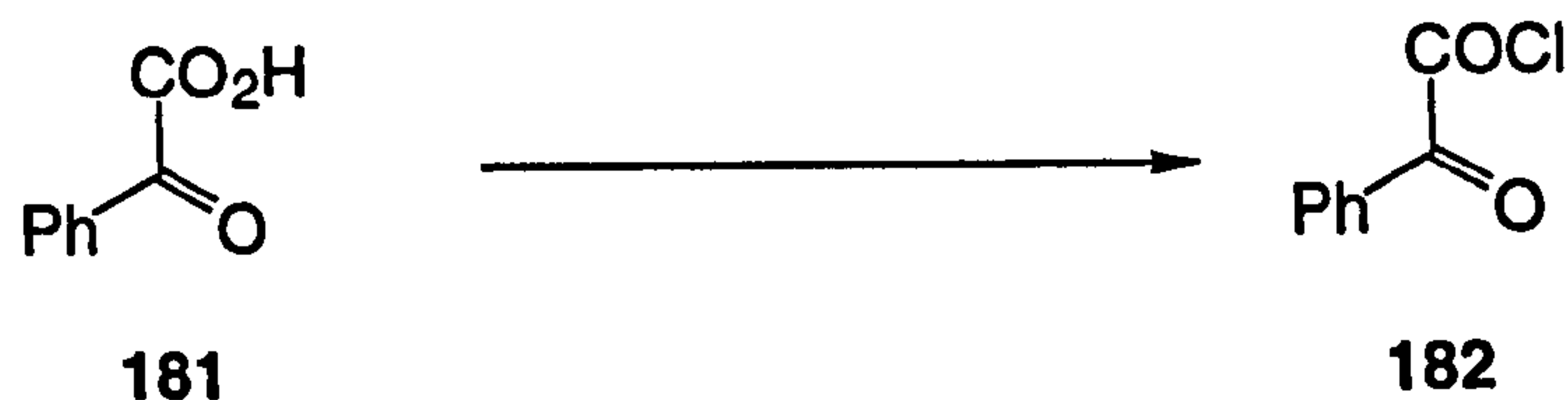
A solution of ethyl benzoylformate **186** (4.46cm³, 28.1mmol), pyridine (2.50cm³, 30.9mmol) and O-benzylhydroxylamine hydrochloride (3.37g, 21.1mmol) in absolute ethanol (50cm³) was heated under reflux for 1 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to afford the title compound **185b** as a clear oil containing a mixture of *E* and *Z* oxime geometric isomers (4.32g, 54%) (11:1 major:minor) from which a sufficient quantity of the major isomer was separated for characterisation. Major isomer: ν_{\max} (film) /cm⁻¹ 2983, 1738, 1447, 1369, 1332, 1220, 1019, 737, 693; δ_{H} (CDCl₃; 400MHz) 1.37 (t, 3H, OCH₂CH₃, *J* 7.2Hz), 4.34 (q, 2H, OCH₂CH₃, *J* 7.2Hz), 5.33 (s, 2H, OCH₂Ph), 7.29-7.44 & 7.60 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 14.2 (OCH₂CH₃), 61.8 (OCH₂CH₃), 76.9 (OCH₂Ph), 126.3, 127.8, 128.0, 128.3, 128.7, 130.3 & 137.3 (Ar-C), 151.2 (PhC=NOBn), 163.7 (CO₂Et); *m/z* 283 (M⁺, 6%), 266 (14%), 180 (6%), 135 (12%), 91 (100%), 77 (52%). Minor isomer: δ_{H} (CDCl₃; 400MHz) 1.37 (t, 3H, *J* 7.2Hz, OCH₂CH₃), 4.44 (q, 2H, *J* 7.2Hz, OCH₂CH₃), 5.29 (s, 2H, OCH₂Ph), 7.29-7.44 & 7.59 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 14.2 (OCH₂CH₃), 62.1 (OCH₂CH₃), 77.9 (OCH₂Ph), 126.3, 127.8, 128.3, 128.7, 130.2, 130.3 & 137.3 (Ar-CH & Ar-C), 151.2 (PhC=NOBn), 163.7 (CO₂Et).²²²

Ethyl 2-phenyl-2-benzyloxyaminoacetate (187b)



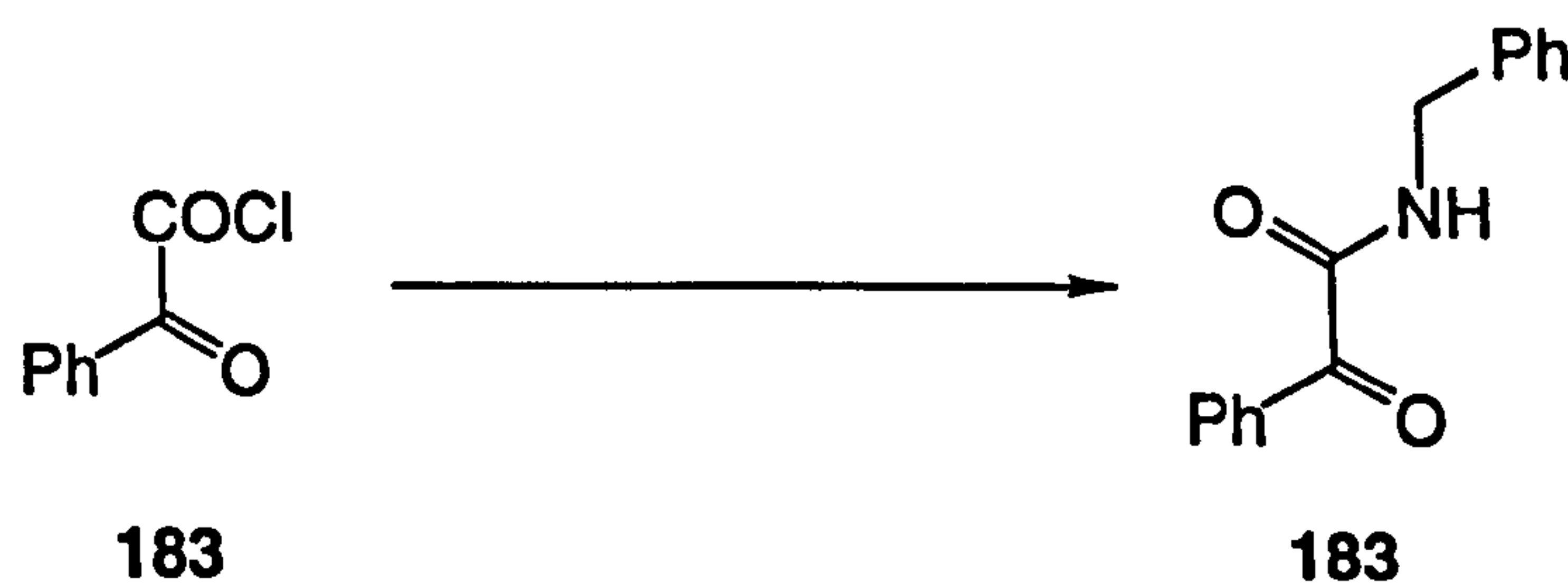
A solution of ethanolic HCl (7M) was prepared by the dropwise addition of acetyl chloride (29.9cm³) to absolute ethanol (50cm³) at 0°C. Using the procedure of Ottenheijm *et al.*,²²² ethyl 2-phenyl-2-benzyloxyiminoacetate **185b** (1.00g, 3.53mmol) was dissolved in this solution (27cm³) which was treated with borane-trimethylamine complex (1.03g, 14.1mmol) in one portion and stirred under an atmosphere of nitrogen for 48 h. To this solution was added sodium carbonate (2.00g, 18.9mmol) before stirring for 5 h, filtering and evaporating the solvent under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to give the title compound **187b** contaminated with the oxime starting material **185b** as a clear film (3:2 respectively, 0.250g **187b**, 25%). A pure sample of the desired product was eventually obtained by preparative reverse phase HPLC (40.0mg); δ_{H} (CDCl₃; 400MHz) 1.28 (t, 3H, *J* 7.2Hz, OCH₂CH₃), 4.23 & 4.30 (each dq, 1H, *J* 7.2, 15.0Hz, OCH₂CH₃), 4.72 (s, 1H, PhCHNHOBn), 4.79 & 4.82 (each d, 1H, *J* 11.6Hz, OCH₂Ph), 7.32-7.41 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 14.0 (OCH₂CH₃), 61.2 (OCH₂CH₃), 67.8 (PhCHNHOBn) 76.3 (OCH₂Ph), 127.8, 127.9, 128.1, 128.5, 128.6 & 128.7 (Ar-CH), 134.0 & 137.6 (Ar-C), 171.9 (CO₂Et) ; *m/z* 286 (MH⁺, 8%), 212 (34%), 104 (12%), 91 (100%).²²²

Benzoylformyl Chloride (182)



A solution of benzoylformic acid **181** (5.00g, 33.3mmol) in DCM (50cm³) was treated with oxalyl chloride (3.20cm³, 36.7mmol) and 5 drops of DMF. After stirring the solution at room temperature for 72 h, the solvent was evaporated under reduced pressure and the residue distilled to yield benzoylformyl chloride **182** as a yellow oil (4.75g, 85%), bp 90-92°C, 3mmHg (lit.,²²¹ 80°C, 3mmHg); ν_{\max} (film) /cm⁻¹ 1775, 1697, 1596, 1581, 1493, 1452, 1257, 1044, 829, 781; δ_{H} (CDCl₃; 400MHz) 7.57 (m, 2H, Ar-H), 7.75 (m, 1H, Ar-H) & 8.01 (m, 2H, Ar-H); δ_{C} (CDCl₃; 100MHz) 129.4, 129.5 & 130.6 (Ar-CH), 136.0 (Ar-C), 166.8 (COCl), 181.2 (PhC=O).

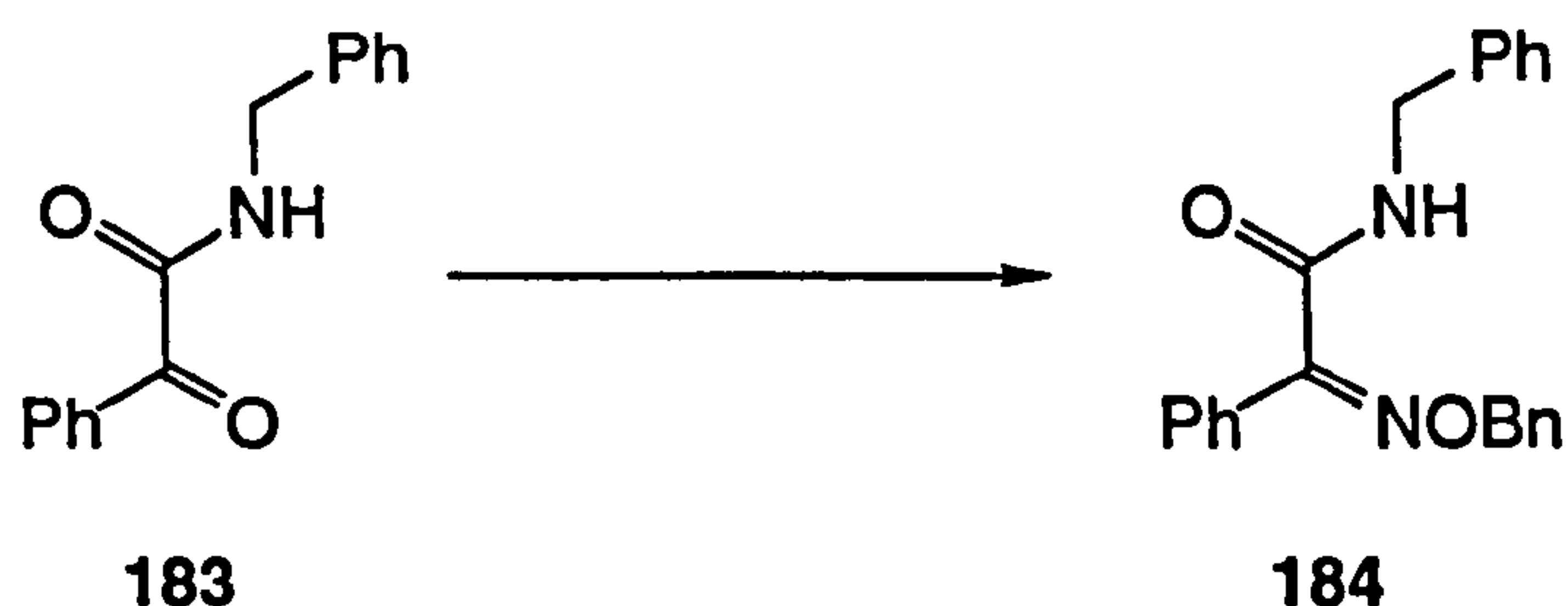
N-Benzylbenzoylformamide (183)



A solution of benzylamine (17.1cm³, 163mmol) and triethylamine (22.7cm³, 163mmol) in DCM (500cm³) was cooled to 0°C before dropwise addition of benzoylformyl chloride **182** (25.0g, 148mmol). The solution was warmed to 20°C and stirred for 18 h then

washed with aqueous HCl (2M; 3 x 250cm³) to yield the title compound **183** as a pale yellow solid (29.1g, 82%), mp 93-96°C (lit.,³²⁶ 92°C) (Found : C, 75.22; H, 5.43; N, 5.86%; M⁺ 239.0947. C₁₅H₁₃NO₂ requires C, 75.30; H, 5.48; N, 5.85%, M⁺ 239.0946); ν_{\max} (KBr) /cm⁻¹ 3263, 3103, 3067, 1685, 1646, 1595, 1572, 1497, 1452, 1431, 1230, 1180, 1033, 945, 689, 675; δ_{H} (CDCl₃; 400MHz) 4.58 (d, 2H, *J* 5.9Hz, NCH₂Ph), 7.26-7.65 (m, 8H, Ar-H), 8.36 (m, 2H, Ar-H); δ_{C} (CDCl₃; 100MHz) 127.9, 128.5, 128.9, 131.2 & 133.3 (Ar-CH), 134.5 & 137.1 (Ar-C), 161.5 (NC=O), 187.5 (PhC=O); *m/z* 240 (MH⁺, 24%), 181 (27%), 107 (28%), 105 (100%), 91 (100%), 77 (57%).

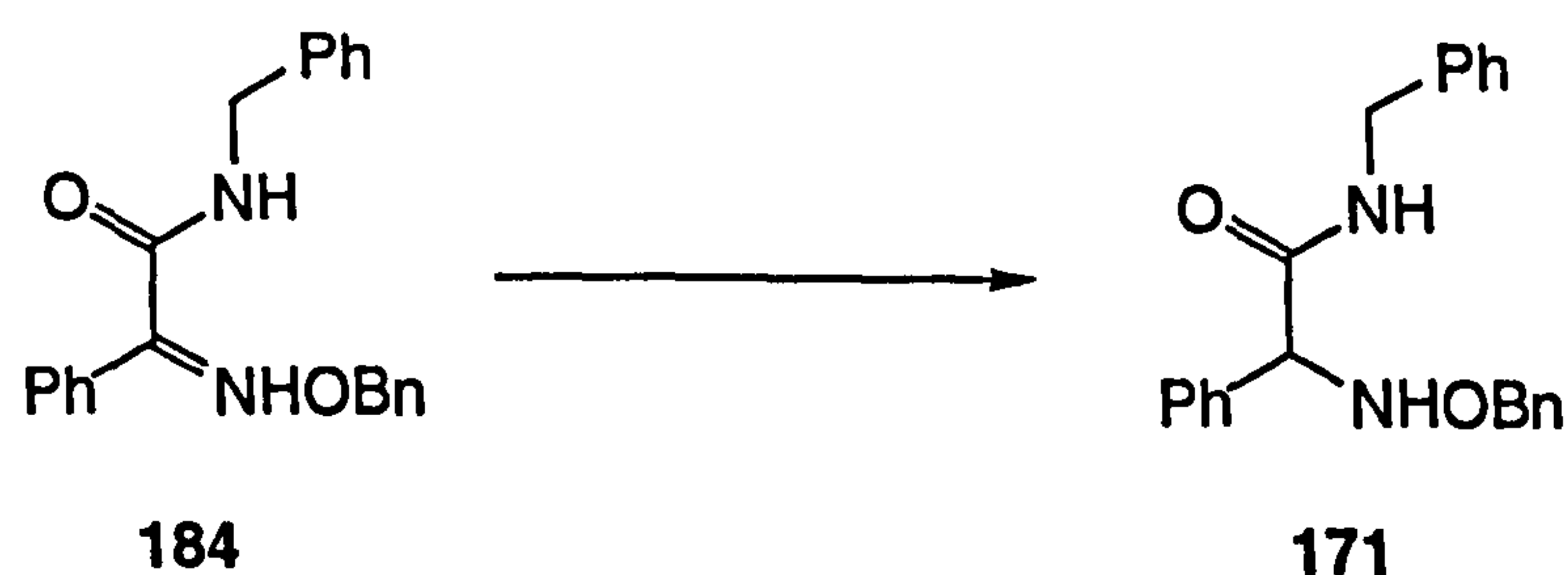
2-Phenyl-2-benzyloxyimino-N-benzylacetamide (**184**)



A solution of N-benzylbenzoylformamide **183** (0.500g, 2.08mmol), O-benzylhydroxylamine hydrochloride (0.330g, 2.08mmol) and triethylamine (0.290cm³, 2.08mmol) in absolute ethanol (20cm³) was heated under reflux for 18 h. The solution was evaporated under reduced pressure before purification by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to yield the *title compound* **184** as white solid containing a mixture of oxime geometric isomers (4.7:1) (0.560g, 80%), mp 148-149°C (Found: C, 76.06; H, 5.84 ; N, 7.95%; M⁺ 344.1506. C₂₂H₂₀N₂O₂ + 0.2H₂O requires C, 75.93; H, 5.85; N, 8.05%; M⁺ 344.1506); (major + minor isomers) *m/z* 345 (MH⁺) (3%), 327 (5%), 237 (5%),

91 (100%). Further careful chromatography allowed separation of a small amount of the major isomer from this mixture for characterisation; ν_{\max} (KBr) / cm^{-1} (major isomer) 3271, 3089, 3064, 3033, 2925, 2877, 1646, 1557, 1455, 1026, 965, 749, 730, 692 ; δ_{H} (CDCl_3 ; 400MHz) (minor isomer) 4.55 (d, 2H, J 6.0Hz, NHCH_2Ph), 5.20 (s, 2H, OCH_2Ph), 7.10 (br s, 1H, NH), 7.25-7.38, 7.40 (m, 15H, Ar-H); (major isomer) 4.62 (d, 2H, J 5.9Hz, NHCH_2Ph), 5.24 (s, 2H, OCH_2Ph), 6.16 (br s, 1H, NH), 7.25-7.38 & 7.68 (m, 15H, Ar-H); δ_{C} (CDCl_3 ; 100MHz) (minor isomer) 43.4 (NHCH_2Ph), 77.4 (OCH_2Ph), 153.1 (PhC=N), 162.9 (NC=O), 127.5, 128.0, 128.7, 129.5 & 129.6 (Ar-CH), 136.8 & 137.3 (Ar-C); (major isomer) 43.4 (NHCH_2Ph), 77.3 (OCH_2Ph), 126.8, 127.6, 128.1, 128.5, 128.6, 128.7 & 130.1 (Ar-CH), 131.1, 136.8 & 137.3 (Ar-C), 153.1 (PhC=N), 162.9 (NC=O).

2-Phenyl-2-benzyloxyamino-N-benzylacetamide (171)

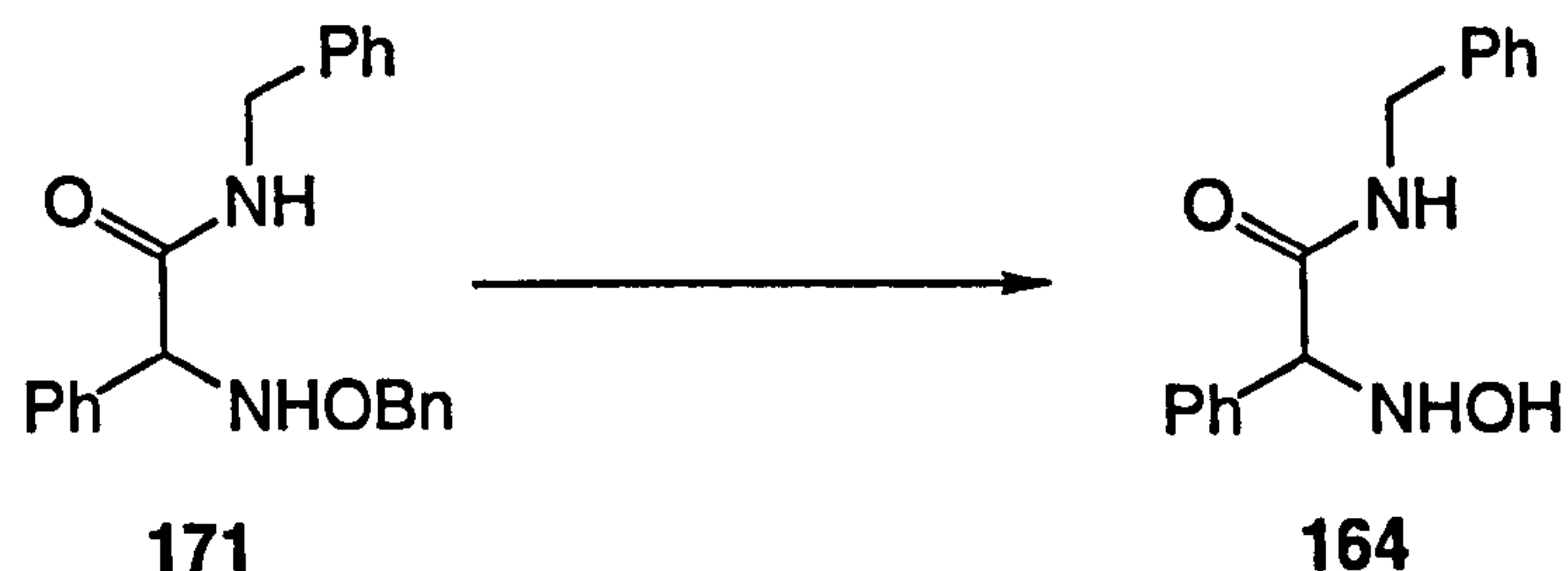


Acetyl chloride (50cm^3) was added to dry ethanol (100cm^3) over 30 min at 0°C under an atmosphere of nitrogen. This solution was then added dropwise to 2-phenyl-2-benzyloxyimino-N-benzylacetamide **184** (4.00g, 11.6mmol) and borane-trimethylamine complex (9.00g, 123mmol) under a nitrogen atmosphere. After stirring at room temperature for 18 h, the solvent was evaporated under reduced pressure and the residue taken up in

(1M solution in THF, 10.1cm³, 10.1mmol) under an atmosphere of nitrogen. After heating at reflux for 2 h, no starting material was detected by TLC analysis, and so the solution was cautiously treated dropwise with aqueous HCl (6M; 25cm³) and stirred for 2 h at 20°C. The solution was then basified with aqueous NaOH (2M) and extracted with DCM (3 x 50cm³) and the organics dried over MgSO₄ before filtering and evaporation to yield pale brown oil consistent with a mixture of the diamine **131** and benzyl alcohol; **N-Benzyl-2-phenyl-1,2-diaminoethane 131**; δ_{H} (CDCl₃; 400MHz) 1.95 (br s, 3H, NH₂ & NH), 2.77 (dd, 1H, *J* 8.4, 11.8Hz, PhCHCHHN), 2.86 (dd, 1H, *J* 4.8, 11.8Hz, PhCHCHHN), 3.82 (s, 2H, NHCH₂Ph), 4.07 (dd, 1H, *J* 4.8, 8.4Hz, PhCHCH₂N), 7.23-7.43 (m, 5H, Ar-H); δ_{C} (CDCl₃; 100MHz) 53.7 & 55.4 (NCH₂Ph & PhCHCH₂N), 56.7 (PhCHCH₂N), 126.4, 126.9, 127.2, 128.0, 128.4 & 128.5 (Ar-CH), 140.2 & 144.4 (Ar-C), identical with an independently prepared sample.³²⁷

An experiment with 4 equivalents of borane-THF complex (based on hydroxylamine **171**) under identical conditions afforded a mixture of the diamine **131**, amino amide **130** and benzyl alcohol. Reducing the amount of borane-THF complex to 1 equivalent returned a mixture of hydroxylamine **171** and amino amide **130** under these conditions. **N-Benzyl-2-phenyl-2-aminoacetamide 130**; δ_{H} (CDCl₃; 400MHz) 4.47 (s, 2H, NHCH₂Ph), 4.60 (m, 1H, PhCHNH₂), 7.23-7.43 (m, 5H, Ar-H); δ_{C} (CDCl₃; 100MHz) 43.2 (NHCH₂Ph), 59.8 (PhCHNH₂), 126.3, 127.8, 127.9, 128.6, 128.8 (Ar-CH), 138.3 & 141.0 (Ar-C), 172.9 (C=O), identical with an independently prepared sample.³²⁷

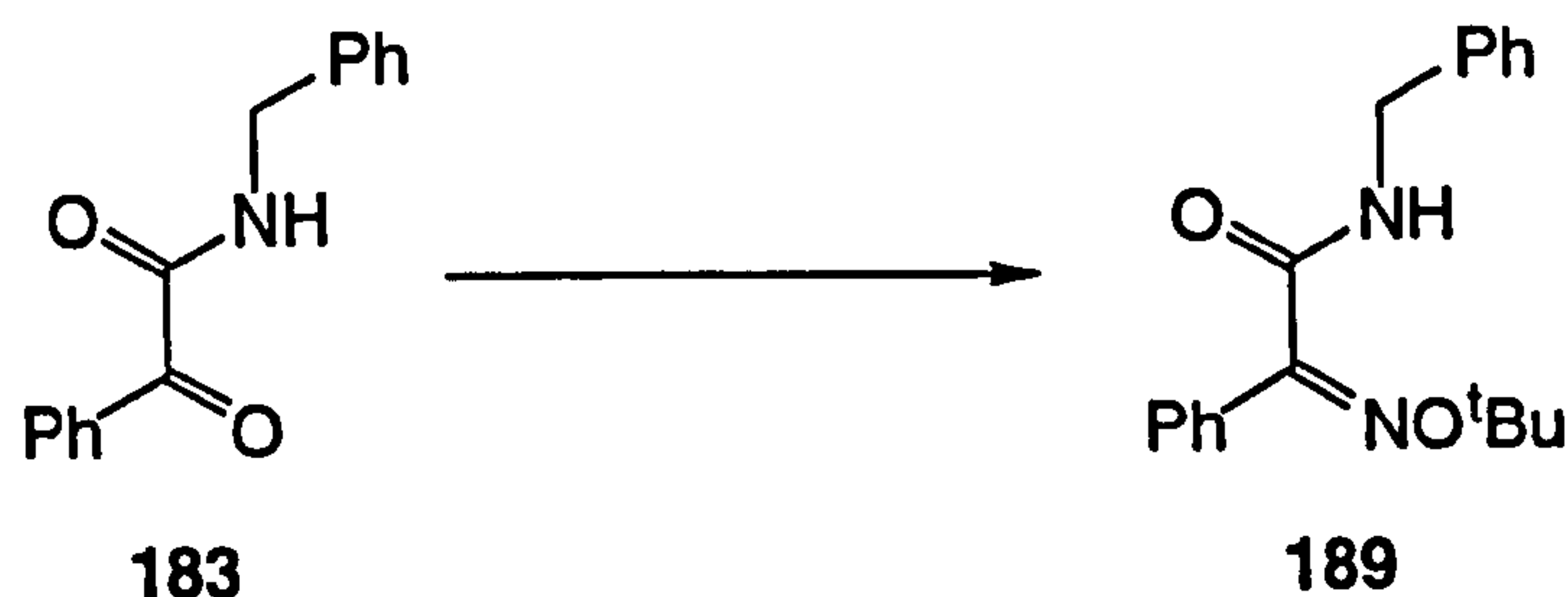
2-Phenyl-2-hydroxyamino-N-benzylacetamide (164)



A solution of 2-phenyl-2-benzyloxyamino-N-benzylacetamide **171** (0.500g, 1.44mmol) in glacial acetic acid (7cm³) was treated with 10% Pd-C (72.0mg, 5mol%) and stirred at 20°C under hydrogen (1 atmos.) for 18 h. The solvent was evaporated under reduced pressure and the residue basified with saturated aqueous NaHCO₃ and extracted with DCM (3 x 30cm³). The combined organic extracts were dried over MgSO₄, filtered then evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the title compound **164** as a white crystalline solid (9.0mg, 2%); δ_{H} (CDCl₃; 400MHz) 1.63 (br s, 1H, NHOH), 3.68 (br s, 1H, NHOH), 4.43 (2 x dd, 2H *J* 5.0, 14.0Hz, NCH₂Ph), 5.07 (s, 1H, PhCHNHOH), 6.53 (br s, 1H, HNC=O), 7.17-7.43 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 43.4 (NCH₂Ph), 74.2 (PhCHNHOH), 126.9, 127.6, 128.7 & 128.9 (Ar-CH), 137.7 & 139.3 (Ar-C), 172.1 (C=O); *m/z* 257 (MH⁺, <1%), 242 (60%), 224 (23%), 196 (17%), 167 (12%), 135 (33%), 108 (59%), 107 (100%), 106 (55%), 91 (82%).

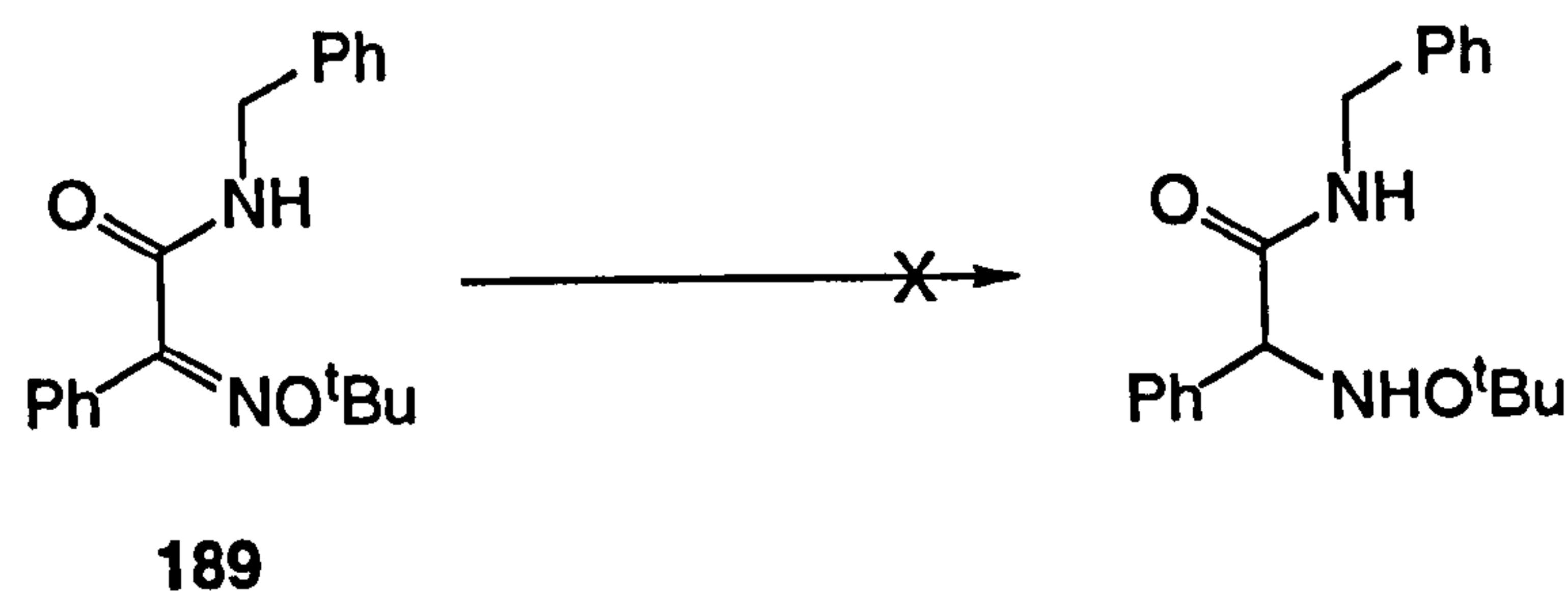
A 48 h reaction time under these conditions again afforded the title compound **164** after chromatography but in a poor yield (4mg, 1%). Changing the solvent to TFA produced, after 2 h under identical conditions, the title compound in a slightly increased yield (14.0mg, 4%).

2-Phenyl-2-*tert*-butoxyimino-N-benzylacetamide (189)



The procedure described above for the preparation of 2-phenyl-2-benzyloxyimino-N-benzylacetamide **184**, was applied to the synthesis of **189** using N-benzylbenzoylformamide **183** (0.950g, 3.98mmol), O-*tert*-butylhydroxylamine hydrochloride (0.500g, 3.98mmol) and triethylamine (0.55cm³, 3.98mmol) in ethanol (50cm³) to afford the *E*- and *Z*- isomers of the *title compound* **189** as a white crystalline solid (0.990g, 81%) after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v), mp 78-80°C (Found: C, 73.54; H, 7.14 ; N, 8.87%; M⁺ 310.1681. C₁₉H₂₂N₂O₂ requires C, 73.52; H, 7.14; N, 9.03%; M⁺ 310.1681); ν_{\max} (KBr) /cm⁻¹ 3257, 3063, 2975, 2936, 1645, 1540, 1365, 1247, 1189, 977, 958, 700, 694; δ_{H} (CDCl₃; 400MHz) major isomer: 1.29 (s, 9H, OC(CH₃)₃), 4.60 (d, 2H, *J* 7.3Hz, NHCH₂Ph), 7.20-7.32 (m, 10H, Ar-H), 7.62 (m, 1H, NH); minor isomer : 1.23 (s, 9H, OC(CH₃)₃), 4.52 (d, 2H, *J* 7.3Hz, NHCH₂Ph), 7.20-7.32 (m, 10H, Ar-H), 7.46 (m, 1H, NH); δ_{C} (CDCl₃; 100MHz) major isomer: 27.5 (OC(CH₃)₃), 43.3 (NHCH₂Ph), 81.0 (OC(CH₃)₃), 126.5-130.0 (Ar-CH), 132.3 & 137.7 (Ar-C), 150.9 (PhC=N), 163.4 (NC=O); *m/z* 311 (MH⁺, 2%), 310 (1%), 254 (23%), 237 (21%), 106 (26%), 104 (30%), 91 (100%).

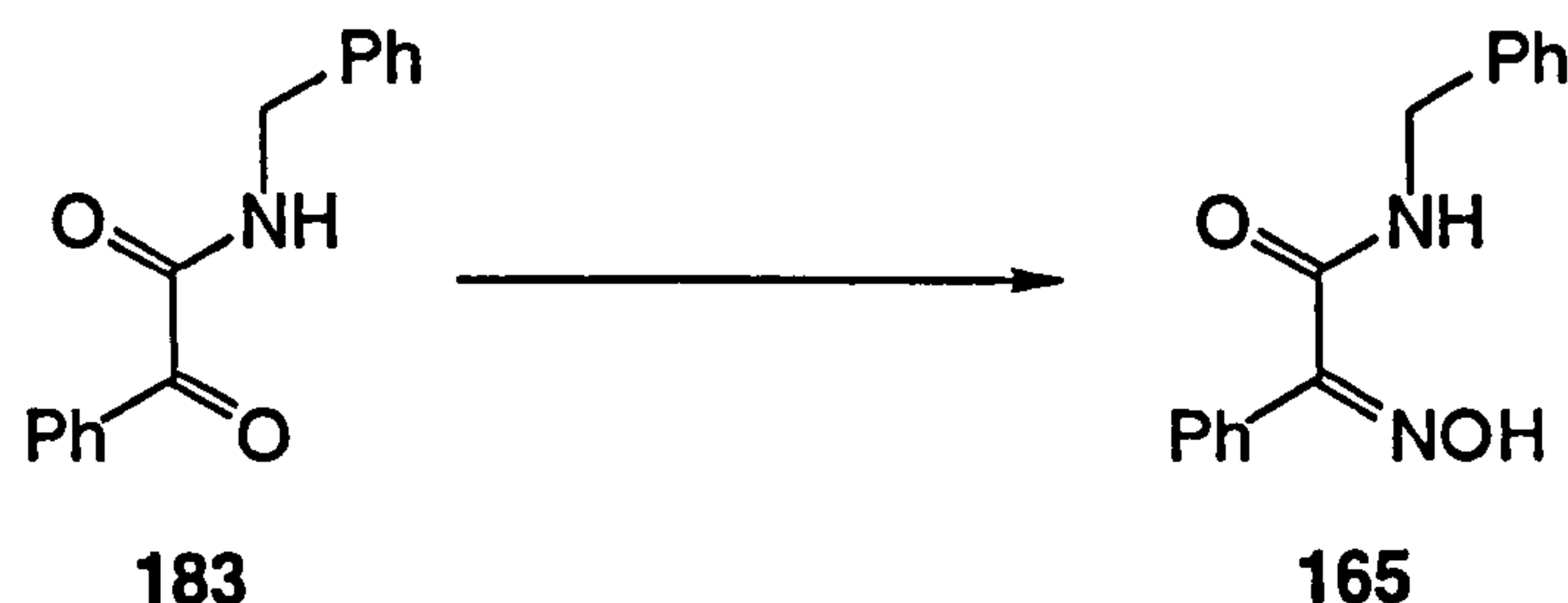
Attempted preparation of 2-phenyl-2-*tert*-butoxyamino-N-benzylacetamide



The method described for the reduction of 2-phenyl-2-benzyloxyimino-N-benzylacetamide **184** was applied to 2-phenyl-2-*tert*-butoxyimino-N-benzylacetamide **189** (0.500g, 1.61mmol) with ethanolic HCl (11M; 8cm³) and borane-trimethylamine complex (0.940g, 12.9mmol). Purification of the resulting mixture afforded unchanged starting material as the only identifiable product.

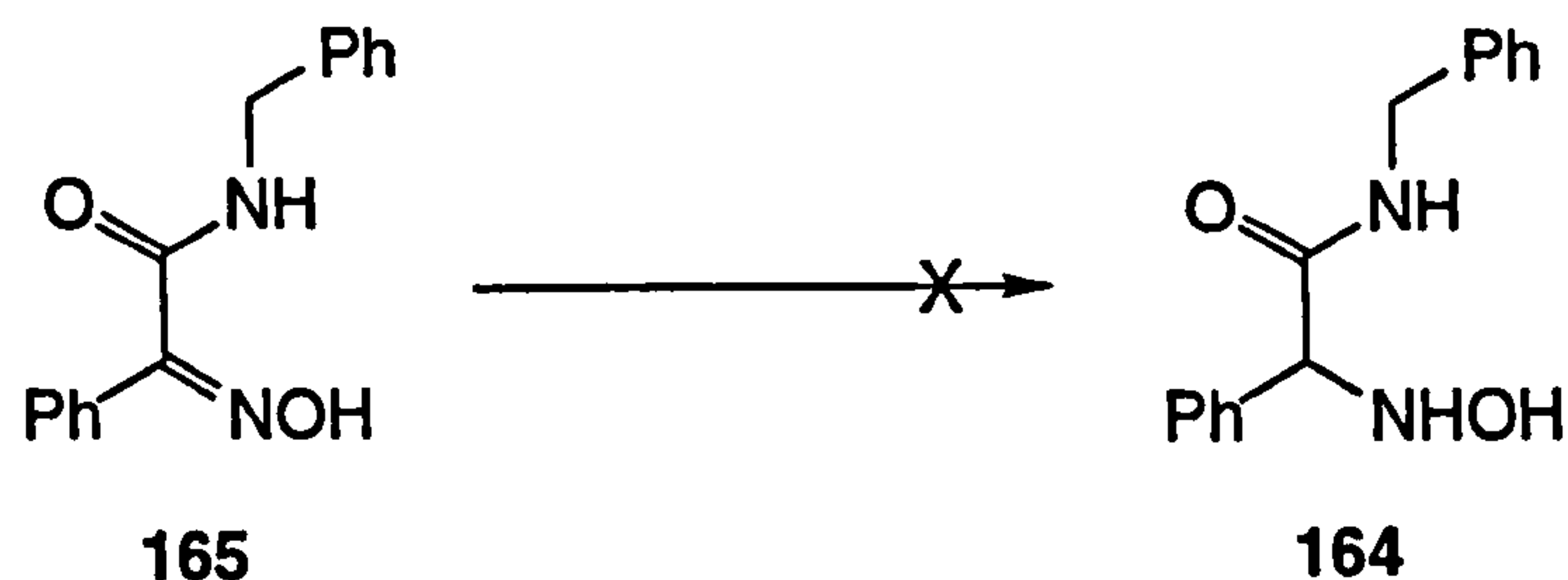
In a separate experiment, a solution of 2-phenyl-2-*tert*-butoxyimino-N-benzylacetamide **189** (0.200g, 0.644mmol) in methanol (10cm³) was treated with NaCNBH₃ (61.0mg, 0.966mmol) in one portion. One drop of bromocresol green indicator was added and the solution brought to a yellow colour (approximately pH3) with methanolic HCl (2M). No reaction was observed by TLC after 2, 24 and 48 h at 20°C or after 48 h at reflux. The mixture was cooled to 20°C and quenched with water (10cm³) before partitioning between DCM and water (100cm³ each). The organic extract was separated, dried over MgSO₄, filtered and evaporated under reduced pressure. The residue was found to contain the starting material **189** only by subsequent NMR spectroscopic analysis.

2-Phenyl-2-hydroxyimino-N-benzylacetamide (165)



Prepared as described above for the preparation of 2-phenyl-2-benzyloxyimino-N-benzylacetamide **184**, using N-benzylbenzoylformamide **183** (2.00g, 8.36mmol), hydroxylamine hydrochloride (1.74g, 25.1mmol) and triethylamine (3.50cm³, 25.1mmol) to afford the *title compound* **165** as a white solid containing a mixture of oxime geometric isomers (major:minor isomer = 1.5:1) (1.20g, 4.72mmol, 56%) after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v), mp 135-137°C (Found: C, 70.99; H, 5.53; N, 10.89%; M⁺ 254.1055. C₁₅H₁₄N₂O₂ requires C, 70.85; H, 5.55; N, 11.02%; M⁺ 254.1055); ν_{\max} (KBr) /cm⁻¹ 3274, 1639, 1608, 1560, 1496, 1455, 1433, 1368, 1255, 996, 943, 689; δ_{H} (d₆-DMSO; 400MHz) (minor isomer) 4.38 (d, 2H, *J* 6.4Hz, NHCH₂Ph), 7.24-7.53 (m, 10H, Ar-H), 8.80 (m, 1H, NHCH₂Ph), 11.87 (s, 1H, NOH); (major isomer) 4.46 (d, 2H, *J* 5.6Hz, NHCH₂Ph), 7.24-7.53 (m, 10H, Ar-H), 9.06 (t, 1H, *J* 6.2Hz, NHCH₂Ph), 11.58 (s, 1H, NOH); δ_{C} (d₆-DMSO; 100MHz) (mixed isomers) 41.8 & 42.2 (NHCH₂Ph), 125.7, 126.7, 126.8, 127.1, 127.2, 127.7, 128.2, 128.3, 128.7, 128.9, 129.3 & 129.4 (Ar-CH), 130.1, 132.3, 139.0 & 139.5 (Ar-C), 150.7 & 152.7 (C=NOH), 163.6 & 164.1 (C=O); *m/z* 254 (3%), 237 (22%), 236 (12%), 106 (27%), 104 (35%), 91 (100%), 77 (22%).

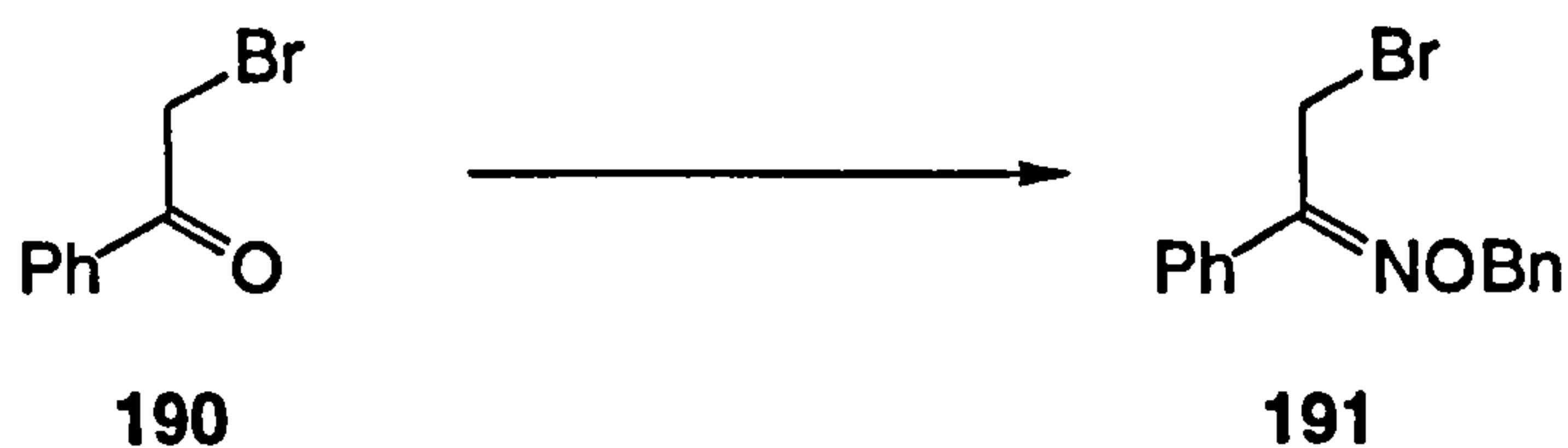
Attempted preparation of 2-phenyl-2-hydroxyamino-N-benzylacetamide (164)



The method described for the reduction of 2-phenyl-2-benzyloxyimino-N-benzylacetamide **184** was applied to 2-phenyl-2-hydroxyimino-N-benzylacetamide **165** (0.500g, 1.97mmol), methanol (25cm³) and NaCNBH₃ (0.190g, 2.95mmol). Overnight reaction at 20°C returned the starting material unchanged. In a similar experiment, a solution of **165** (0.270g, 1.06mmol) in THF (10cm³) was treated with NaCNBH₃ (1M solution in THF, 1.17cm³, 1.17mmol) and acidified with 2 drops of methanolic HCl (2M). No reaction was observed after 5 h at 20°C, nor was reaction evident after addition of further NaCNBH₃ solution (2.50cm³, 2.50mmol), re-acidification and stirring for 18 h.

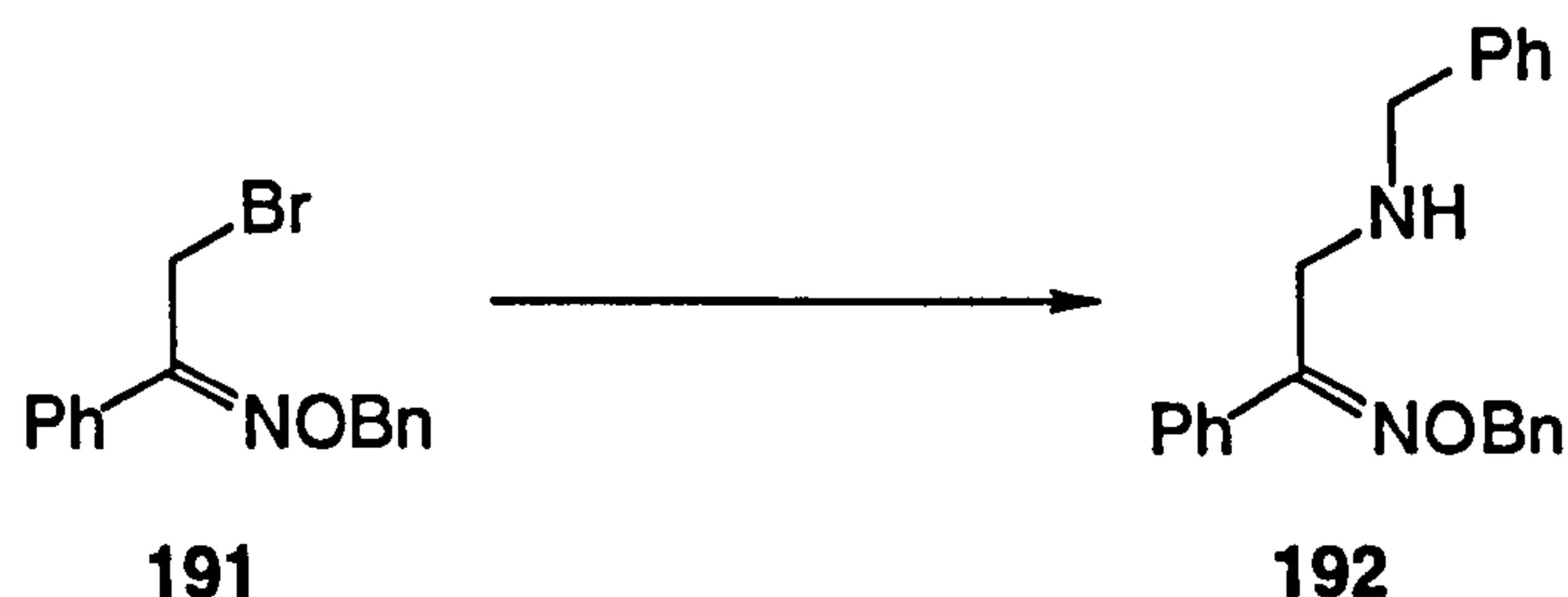
Similarly, a solution of **165** (0.130g, 0.51mmol) in dry distilled THF (10cm³) at 0°C under an atmosphere of nitrogen was treated with borane-THF complex (1M solution in THF, 2.04cm³, 2.04mmol) and stirred at 20°C overnight. The solution was cooled to 0°C and cautiously treated with aqueous HCl (6M; 5cm³) before warming to 60°C for 1 h. The solution was basified with aqueous NaOH (2M) and extracted with ether (3 x 30cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure but the residue contained none of the desired product **164**.

2-Bromoacetophenone O-benzyloxime (191)



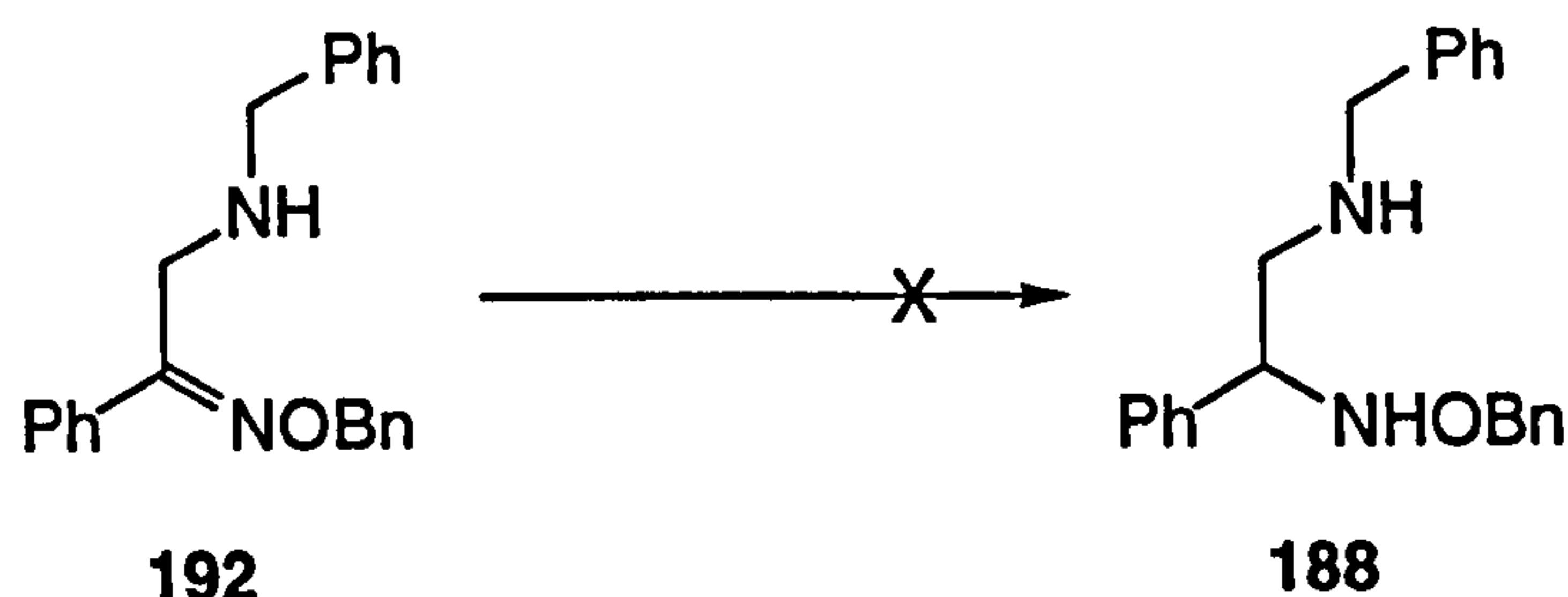
A solution of 2-bromoacetophenone **190** (5.00g, 25.1mmol) in ethanol (250cm³) was treated with O-benzylhydroxylamine hydrochloride (4.41g, 27.6mmol) and triethylamine (3.84cm³, 27.6mmol). After heating under reflux for 2 h, the solvent was evaporated under reduced pressure and the crude product **191** obtained as a mixture of geometric isomers (major:minor = 5.25:1) by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) and used directly; δ_{H} (CDCl₃; 400MHz) major isomer: 4.57 (s, 2H, BrCH₂C=N), 5.31 (s, 2H, OCH₂Ph), 7.30-7.46 (m, 8H) & 7.70 (m, 2H, Ar-H); minor isomer: 4.39 (s, 2H, BrCH₂C=N), 5.32 (s, 2H, OCH₂Ph), 7.30-7.46 (m, 8H) & 7.70 (m, 2H, Ar-H); δ_{C} (CDCl₃; 100MHz) major isomer: 32.7 (BrCH₂C=N), 76.9 (OCH₂Ph), 126.2, 128.0, 128.1, 128.2, 128.4 & 129.7 (Ar-CH), 133.4 & 137.4 (Ar-C), 152.9 (C=N).

2-(N-Benzylamino)acetophenone O-benzyloxime (192)



A solution of the crude 2-bromoacetophenone O-benzyloxime **191** (7.64g, ≈ 25.1 mmol) in chloroform (200cm³) was treated with benzylamine (8.23cm³, 75.3mmol) and heated under reflux for 18 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to yield the separated *oxime isomers* of **192** as pale yellow oils (4.68g, 56% from 2-bromoacetophenone **190**) (major:minor isomer = 8:1) (Found: M^+ 331.1810. C₂₂H₂₂N₂O requires M^+ 331.1810); ν_{\max} (film) /cm⁻¹ 3062, 3029, 2925, 2874, 1496, 1454, 1364, 923, 737, 696; δ_{H} (CDCl₃; 400MHz) major isomer: 1.69 (br s, 1H, NH), 3.74 (s, 2H, NHCH₂Ph), 3.90 (s, 2H, PhCCH₂N), 5.25 (s, 2H, OCH₂Ph), 7.21-7.41 (m, 12H, Ar-H), 7.63 (m, 3H, Ar-H); minor isomer: 1.69 (br s, 1H, NH), 3.56 & 3.68 (each s, 2H, NHCH₂Ph & PhCCH₂N), 5.15 (s, 2H, OCH₂Ph), 7.21-7.42 (m, 15H, Ar-H), 7.63 (m, 3H, Ar-H); δ_{C} (CDCl₃; 100MHz) major isomer: 44.2 (PhCCH₂N), 53.3 (NHCH₂Ph), 76.7 (OCH₂Ph), 126.5, 126.9, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6 & 129.2 (Ar-CH), 135.1, 137.6 & 139.8 (Ar-C), 157.4 (PhC=N); minor isomer: 52.1 & 52.7 (PhCCH₂N & NHCH₂Ph), 76.0 (OCH₂Ph), 127.0, 127.6, 127.9, 128.0, 128.2, 128.3, 128.3 & 129.0 (Ar-CH), 132.7, 138.2 & 139.7 (Ar-C), 155.3 (C=N); m/z 331 (MH⁺, 45%), 223 (41%), 210 (12%), 120 (52%), 91 (100%).

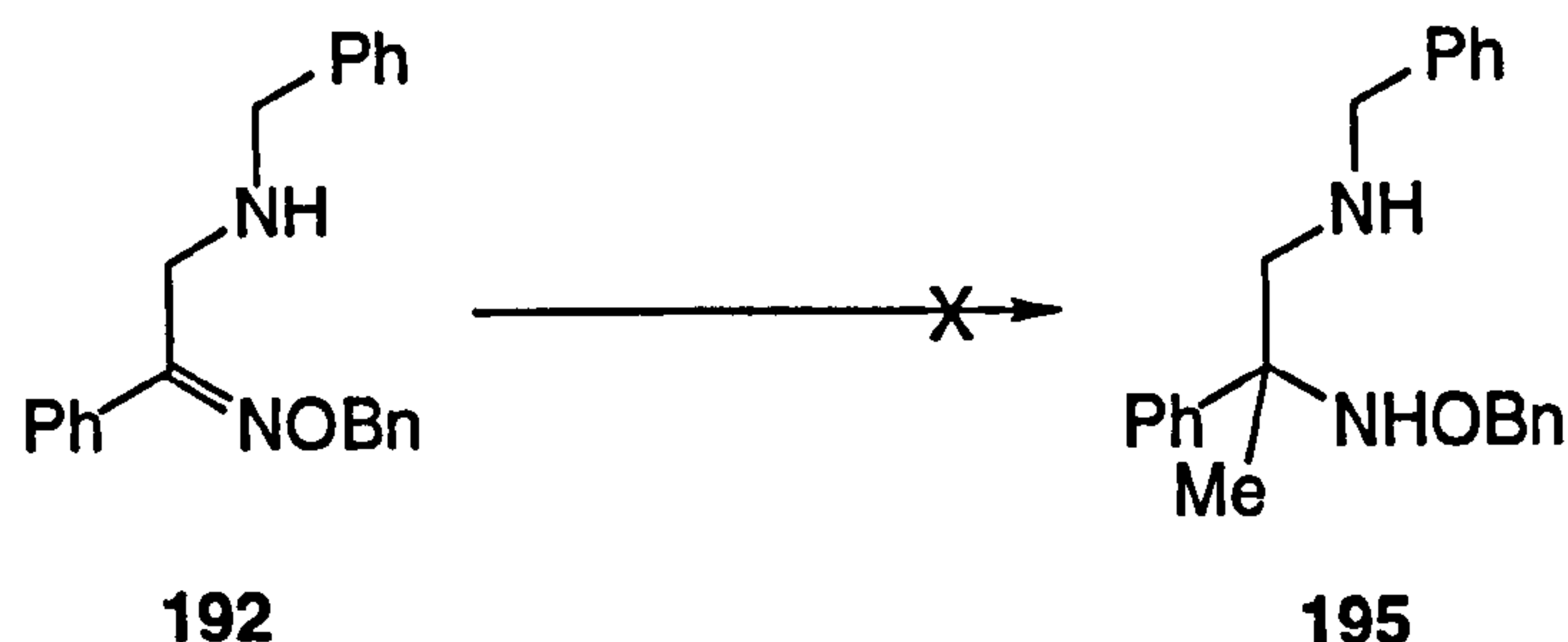
Attempted preparation of N-benzyl-2-benzyloxyamino-2-phenylethylamine (188)



The method used in the reduction of 2-phenyl-2-benzyloxyimino-N-benzylacetamide **184** was applied to 2-(N-benzylamino)acetophenone O-benzyloxime **192** (0.670g, 2.03mmol), using ethanolic HCl (11M; 10cm³) and borane-trimethylamine complex (0.590g, 8.12mmol). However, the isolated residue contained only unchanged starting material.

In a separate experiment, this reduction was undertaken using the method applied to the attempted reduction of 2-phenyl-2-(hydroxyimino)-N-benzylacetamide **165**, using **192** (1.00g, 3.03mmol), methanol (50cm³), bromocresol green (10 drops) and NaCNBH₃ (0.290g, 4.55mmol), keeping the solution acidic with dropwise addition of methanolic HCl (2M). The solution was unchanged by TLC analysis after 18 h at 20°C and, after work-up, afforded the starting material **184** only.

**Attempted preparation of N-benzyl-2-benzyloxyamino-2-phenylpropylamine
(195)**

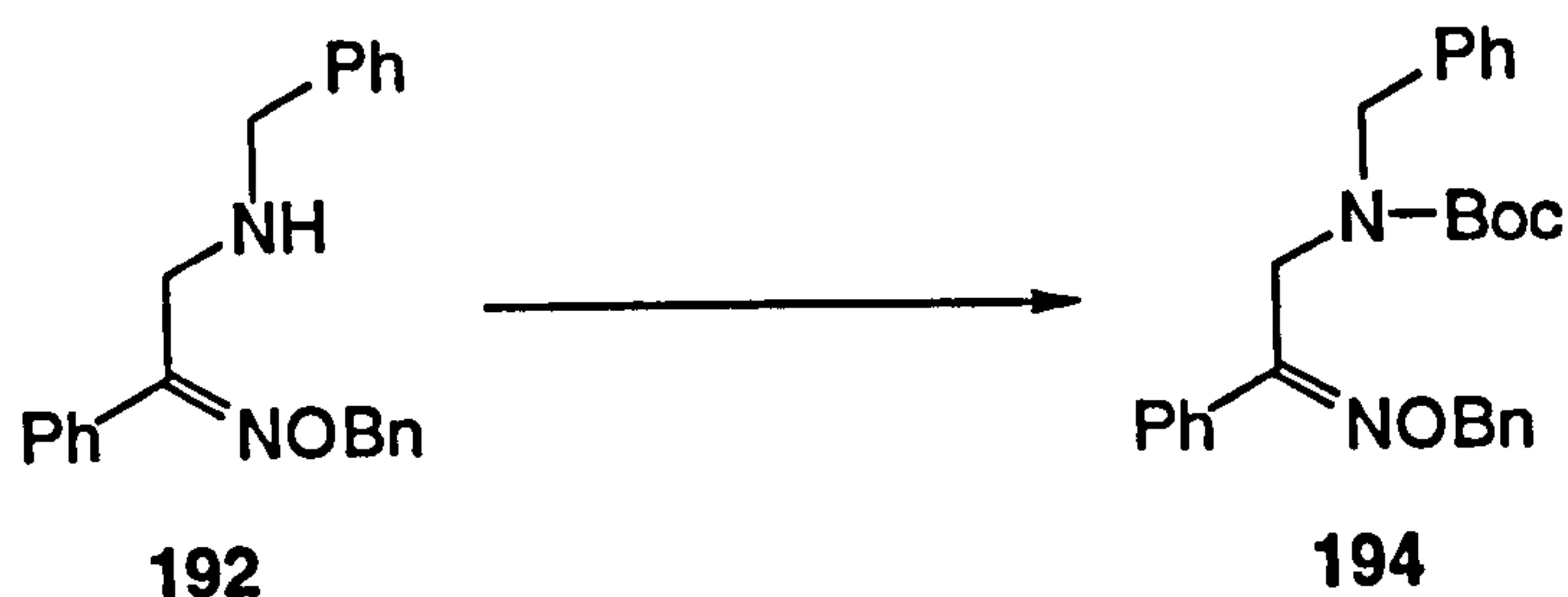


A solution of 2-(N-benzylamino)acetophenone O-benzyloxime **192** (0.200g, 0.610mmol) in anhydrous ether (10cm³) was treated with methyl lithium (1.6M solution in ether, 1.82cm³, 2.92mmol) at 0°C dropwise. After stirring at 0°C for 1 h, the reaction was quenched with water (2cm³) and the solution warmed to 20°C. The organic layer was washed with water (2 x 20cm³), dried over MgSO₄, filtered and evaporated under reduced pressure. However, the residue yielded none of the desired material **195** after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v).

In a separate experiment, a solution of 2-(N-benzylamino)acetophenone O-benzyloxime **192** (0.50g, 1.51mmol) in anhydrous ether (10cm³) was cooled to -75°C before dropwise treatment with boron trifluoride etherate (2.80cm³, 22.1mmol) keeping the temperature below -70°C. This turbid mixture was stirred for 15 min at -75°C before slow dropwise addition of methyl lithium (1.6M solution in ether, 2.80cm³, 4.5mmol) over 10 min. After stirring at -75°C for 5 h, the solution was quenched with water (1cm³) and warmed to 20°C for 18 h. The residue was partitioned between DCM and water (20cm³ each) and the aqueous phase separated and further extracted with DCM (3 x 20cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced

pressure. Column chromatography of the residue (SiO₂, hexane:EtOAc 2:1 v/v) afforded none of the desired product **195**.

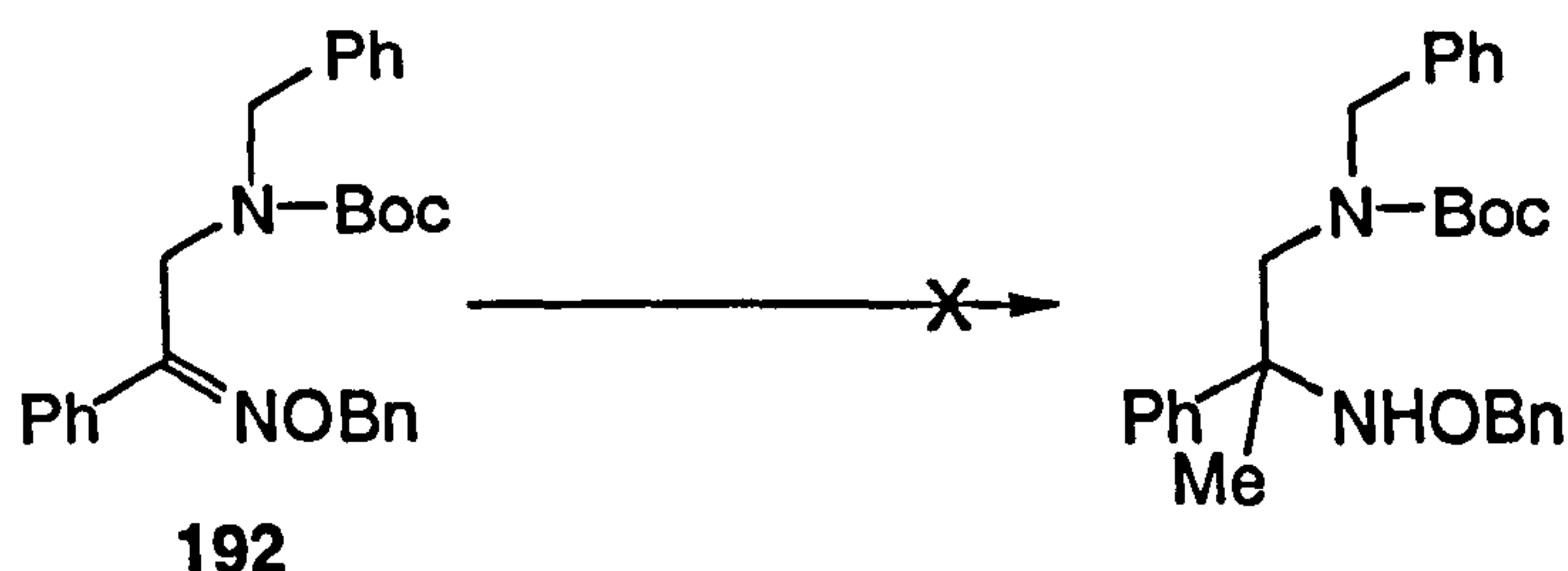
2-(N-Benzyl-N-*tert*-butoxycarbonyl)aminoacetophenone O-benzyloxime
(194)



A solution of 2-(N-benzylamino)acetophenone O-benzyloxime **192** (0.250g, 0.760mmol) in DCM (10cm³) at 0°C was treated with triethylamine (0.210cm³, 1.52mmol) and di-*tert*-butyl dicarbonate (0.180g, 0.84mmol) under an atmosphere of nitrogen. The solution was warmed to 20°C overnight, before partitioning between DCM (30cm³) and aqueous citric acid (1M; 30cm³). The phases were separated and the organic layer was washed with further citric acid solution (3 x 30cm³) before drying over MgSO₄, filtering and evaporation under reduced pressure to afford the *title compound* **194** as a colourless oil (150mg, 0.348mmol, 46%). Its existence as a mixture of carbamate rotamers was shown by ¹H NMR spectroscopic analysis. Subsequent variable-temperature ¹H NMR spectroscopic analysis of **194** in d₆-DMSO showed signal-doubling of the two N-CH₂ groups to collapse as the temperature was raised to 50°C, becoming sharp singlets by 80°C, (Found: C, 75.30; H, 7.29; N, 6.49%; MH⁺ 431.2333. C₂₇H₃₀N₂O₃ requires C, 75.32; H, 7.02; N, 6.50%; MH⁺ 431.2334); ν_{max} (KBr) /cm⁻¹ 2968, 1695, 1449, 1416, 1366, 1241, 1158, 1119, 1028,

923, 746, 699; δ_{H} (d_6 -DMSO; 400MHz) 1.27 (s, 9H, $\text{C}(\text{CH}_3)_3$), 4.01 & 4.23, 4.48 & 4.59 (4 x br s, each pair 2H, PhCHCH_2N & NHCH_2Ph), 5.14 (br s, 2H, NOCH_2Ph), 7.08-7.54 (m, 15H, Ar-H); δ_{H} (d_6 -DMSO; 400MHz, 95°C) 4.18 & 4.56 (2 x s, each 2H, PhCHCH_2N & NHCH_2Ph), 5.16 (s, 2H, NOCH_2Ph), (Ar-H not measured); m/z 374 ($\text{M}^+ - \text{Bu} + \text{H}^+$, 1%), 225 (7%), 223 (6%), 212 (4%), 208 (5%), 184 (5%), 167 (7%), 156 (5%), 120 (9%), 91 (100%), 57 (24%).

Attempted preparation of N-benzyl-N-*tert*-butoxycarbonyl-2-(benzyloxyamino)-2-phenylpropylamine

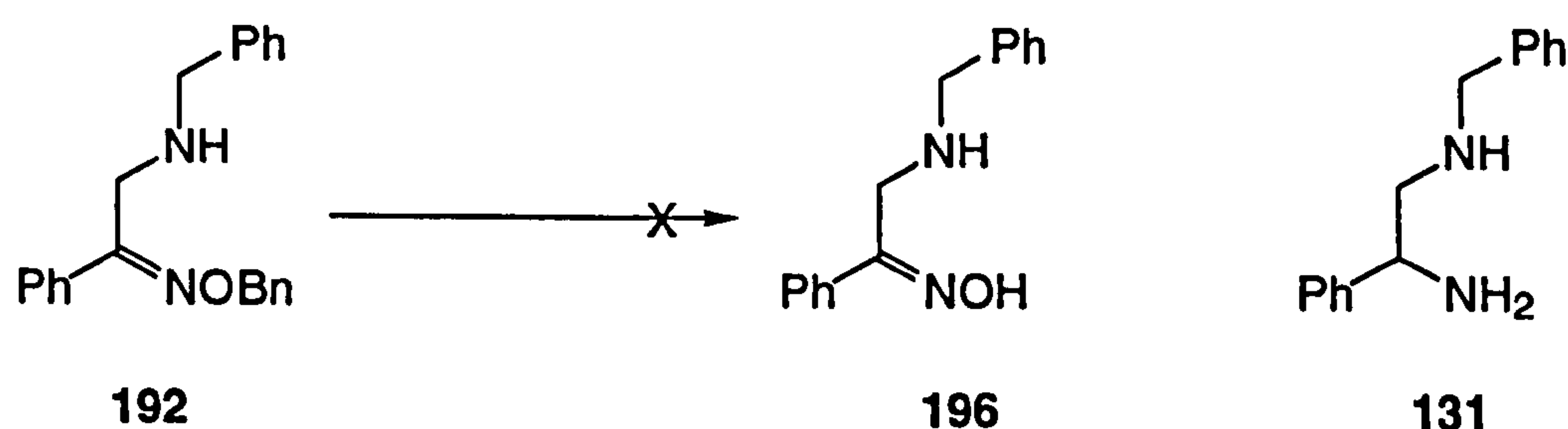


A solution of 2-(N-benzyl-N-*tert*-butoxycarbonyl)aminoacetophenone O-benzyloxime **194** (0.100g, 0.232mmol) in anhydrous ether at -78°C under an atmosphere of nitrogen was treated with methyl lithium (1.6M solution in ether, 0.475cm³, 0.760mmol) and stirred for 2 h before warming to ambient temperature and quenching with water (2cm³). The organic layer was washed with water (3 x 5cm³) before drying over MgSO_4 , filtration and evaporation under reduced pressure to yield a brown film from which no desired material was isolated by column chromatography (SiO_2 , hexane:EtOAc 2:1 v/v).

This experiment was repeated with addition of boron trifluoride etherate (1.39cm³, 10.9mmol) to a solution of 2-(N-benzyl-N-*tert*-butoxycarbonyl)aminoacetophenone O-

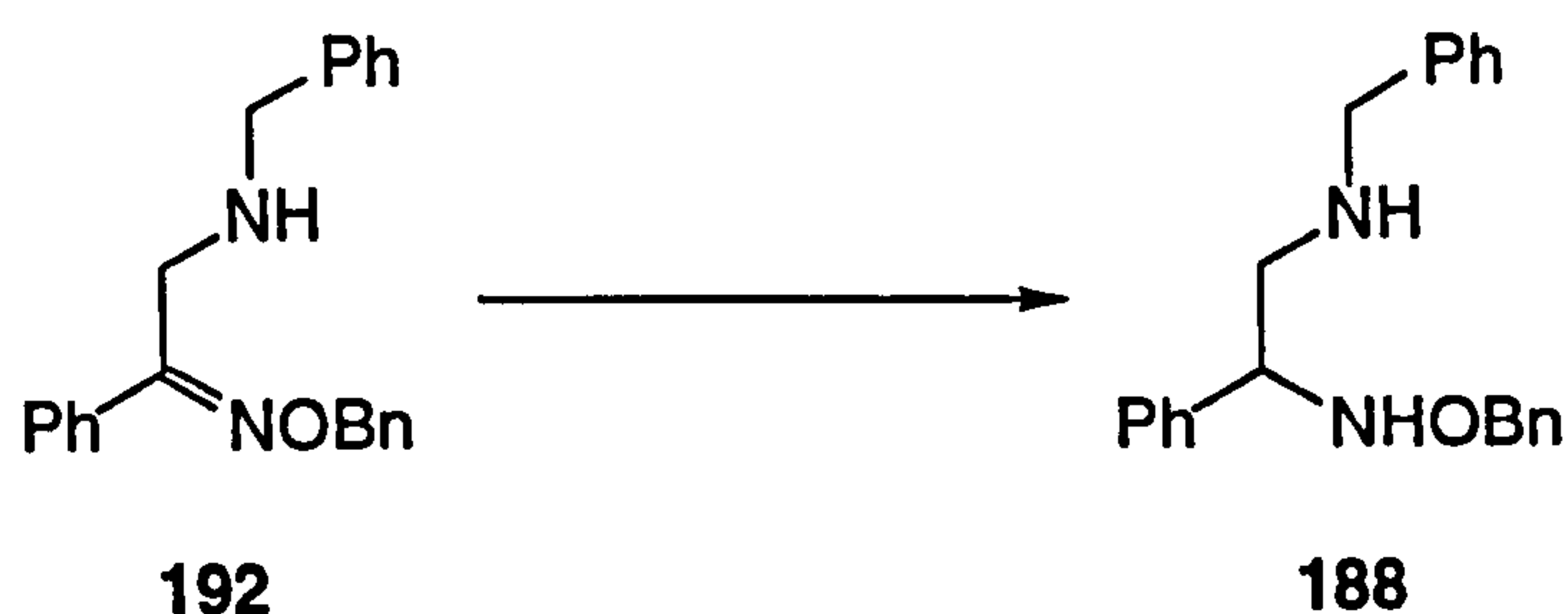
benzyloxime **194** (0.200g, 0.464mmol) in anhydrous ether (10cm³) at -78°C. The solution was stirred for 30 min before dropwise addition of methyl lithium (1.6M solution in ether, 0.87cm³, 1.39mmol). After 1.5 h, no reaction was observed by TLC analysis and so the mixture warmed to -10°C for a further 1.5 h. Treatment as described above furnished a brown residue was from which none of the title compound was isolated after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v).

Attempted preparation of 2-(N-benzylamino)acetophenone oxime (**196**)



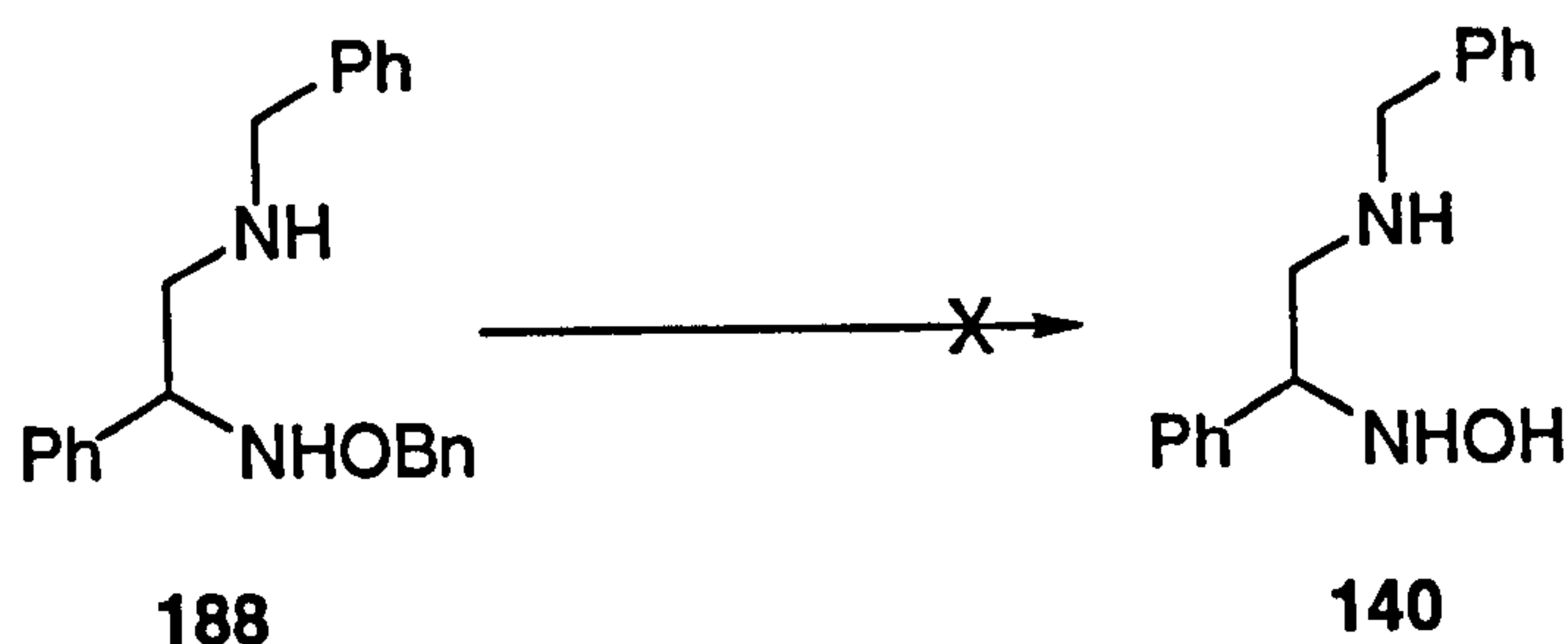
By the method of Corey *et al*,²⁴⁸ a mixture of 2-(N-benzylamino)acetophenone O-benzyloxime **192** (0.200g, 0.605mmol) and 10% Pd-C (32mg, 5mol%) in methanol (10cm³) was stirred under hydrogen (1 atmos.) at 20°C and atmospheric pressure for 2.5 h by which time no starting material remained by TLC analysis. The mixture was filtered, the catalyst residue washed with methanol (2 x 10cm³) and the filtrate evaporated under reduced pressure. The residue was found to contain not the desired oxime **196**, but a mixture of diamine **131** identical with a known sample,³²⁷ and benzyl alcohol.

N-Benzyl-2-benzyloxyamino-2-phenylethylamine (188)



A solution of 2-(N-benzylamino)acetophenone O-benzyloxime **192** (2.00g, 6.05mmol) in dry THF (40cm³) was treated with borane-THF complex (1M solution in THF, 12.1cm³, 12.1mmol) at 0°C under a nitrogen atmosphere. The solution was warmed to 20°C for 4 h then slowly treated with aqueous HCl (2M; 20cm³) and heated to 60°C for 2 h. After cooling to room temperature, the reaction was basified with aqueous sodium hydroxide (2M) and extracted with ether (3 x 30cm³). The combined organic extracts were dried over MgSO₄, before filtration then evaporation under reduced pressure and purification of the residue by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to yield the *desired product* **188** as a yellow oil (1.59g, 79%) (Found: C, 79.65, H, 7.09, N, 8.41%; MH⁺ 333.1967. C₂₂H₂₄N₂O requires C, 79.48, H, 7.28, N, 8.43%; MH⁺ 333.1967); ν_{\max} (film) /cm⁻¹ 3062, 3029, 2910, 2853, 1495, 1453, 1362, 1028, 747; δ_{H} (CDCl₃; 400MHz) 2.87 (m, 2H, PhCHCH₂N) 3.78 (2 x d, 2H, *J* 13.2Hz, NHCH₂Ph), 4.18 (dd, 1H, *J* 5.6, 8.4Hz, PhCHNHOBn), 4.59 (2 x d, 2H, *J* 11.2Hz, OCH₂Ph), 7.18-7.41 (m, 15H, Ar-H); δ_{C} (CDCl₃; 100MHz) 52.2 (PhCHCH₂N), 53.7 (NHCH₂Ph), 65.0 (PhCHNHOBn), 76.7 (OCH₂Ph), 126.9, 127.6, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4 & 128.6 (Ar-CH), 137.2, 140.1 & 140.7 (Ar-C); *m/z* 333 (MH⁺, 3%), 212 (6%), 120 (35%), 106 (53%), 91 (100%).

Attempted preparation of N-benzyl-2-hydroxyamino-2-phenylethylamine (140)



N-Benzyl-2-benzyloxyamino-2-phenylethylamine **188** was subjected to a number of debenzylation strategies in attempts to afford **140**, none of which afforded the desired material. The individual reagents and condition are outlined below.

10% Pd-C : A mixture of N-benzyl-2-benzyloxyamino-2-phenylethylamine **188** (0.200g, 0.610mmol) and 10% Pd-C (30.0mg, 5mol%) in methanol (20cm³) was stirred under hydrogen at 20°C (1 atmos.) for 18 h. The mixture was filtered and the filtrate evaporated to afford a mixture of diamine **131** and benzyl alcohol.

10% Pd-C / H⁺ : A mixture of N-benzyl-2-benzyloxyamino-2-phenylethylamine **188** (0.200g, 0.610mmol) and 10% Pd-C (30.0mg, 5mol%) in glacial acetic acid (20cm³) was stirred under hydrogen at 20°C (1 atmos.) for 18 h. The mixture was filtered and basified with aqueous NaOH (2M) before extraction with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to afford diamine **131** along with benzyl alcohol. This experiment was repeated using an atmosphere of hydrogen at 15psi of pressure and at 20°C which afforded an intractable mixture of products.

Raney Nickel : By the procedure reported by Horita *et al.*,²⁴⁰ a mixture of N-benzyl-2-benzyloxyamino-2-phenylethylamine **188** (0.260g, 0.780mmol) and W-2 Raney

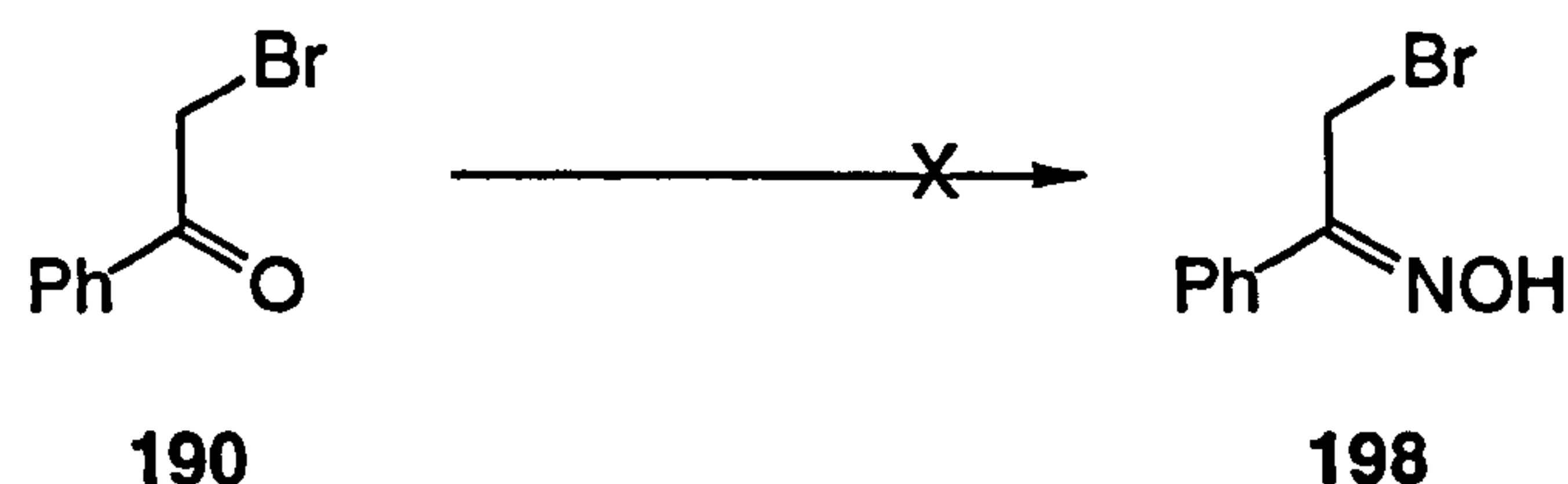
Nickel (0.260g) in methanol (20cm³) was stirred under hydrogen at 20° (1 atmos.) for 72 h but returned the starting material unchanged.

10% Pd-C / ammonium formate : By the method of Bieg and Szeja,²⁴² a mixture of N-benzyl-2-benzyloxyamino-2-phenylethylamine **188** (0.100g, 0.300mmol), ammonium formate (0.100g, 1.59mmol) and 10% Pd-C (0.180g, 56mol%) in methanol (20cm³) was heated under reflux under nitrogen (1 atmos.) for 18 h but only returned a complex mixture of unidentifiable products.

Boron tris-trifluoroacetate : The B(TFA)₃ reagent was prepared by the method of Pless and Bauer³²⁸ by treatment of dry DCM (100cm³) with distilled anhydrous TFA (9.20cm³, 120mmol) and boron tribromide (3.80cm³, 39.9mmol) under nitrogen at 0°C to form an instantaneous white precipitate. The solvent was then removed under reduced pressure before addition of this solid (1.50g, 4.97mmol) to a solution of N-benzyl-2-benzyloxyamino-2-phenylethylamine **188** (0.200g, 0.602mmol) in distilled anhydrous TFA (5cm³). The mixture was stirred at ambient temperature for 18 h before evaporation of the solvent under reduced pressure and basifying with aqueous NaOH (2M) and extraction with DCM (3 x 30cm³). The organics were dried over MgSO₄, filtered and evaporated under reduced pressure to return unchanged starting material.

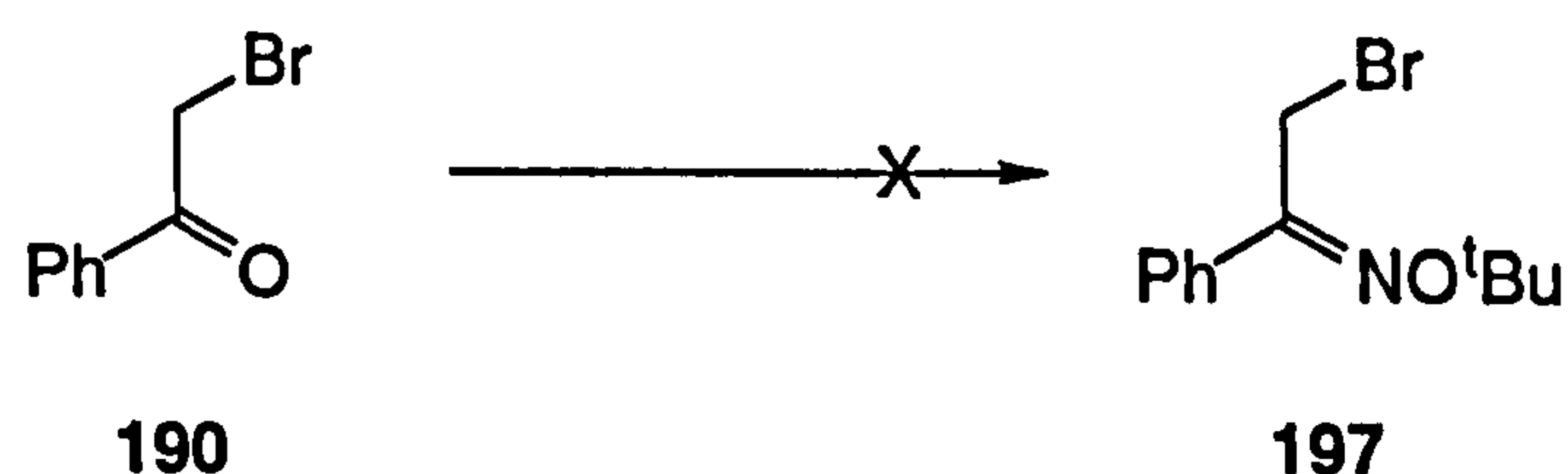
30% HBr / acetic acid : A solution of N-benzyl-2-benzyloxyamino-2-phenylethylamine **188** (0.130g, 0.391mmol) in glacial acetic acid (5cm³) was treated with HBr in acetic acid (30% w/v; 5cm³) and heated under reflux for 18 h. The solution was diluted with water (10cm³) and extracted with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to return the starting material unchanged.

Attempted preparation of 2-bromoacetophenone oxime (198)



A solution of 2-bromoacetophenone **190** (5.00g, 25.1mmol), hydroxylamine hydrochloride (1.91g, 27.5mmol) and triethylamine (3.85cm³, 27.5mmol) in ethanol (200cm³) was heated to reflux for 48 h before removal of the solvent under reduced pressure. The residue yielded none of the desired material **198** by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v).

Attempted preparation of 2-bromoacetophenone *O*-*tert*-butyloxime (197)



A solution of 2-bromoacetophenone **190** (0.810g, 4.06mmol), *O*-*tert*-butylhydroxylamine hydrochloride (0.510g, 4.06mmol) and triethylamine (1.13cm³, 8.12mmol) in ethanol (50cm³) was heated to reflux for 18 h. After cooling to 20°C, the solution was evaporated at reduced pressure but column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) failed to afford the title compound **197**.

Similarly, a mixture of **190** (0.400g, 2.01mmol), *O-tert*-butylhydroxylamine hydrochloride (0.250g, 1.99mmol) and sodium acetate (0.330g, 0.402mmol) in water (20cm³) was heated to 50°C. After 18 h, the mixture was cooled to 20°C to afford a complex mixture of products from which the desired material was not isolated. This experiment was then repeated, with methanol as the solvent (10cm³) and stirring for 18 h at 20°C, but this only afforded an intractable mixture of products.

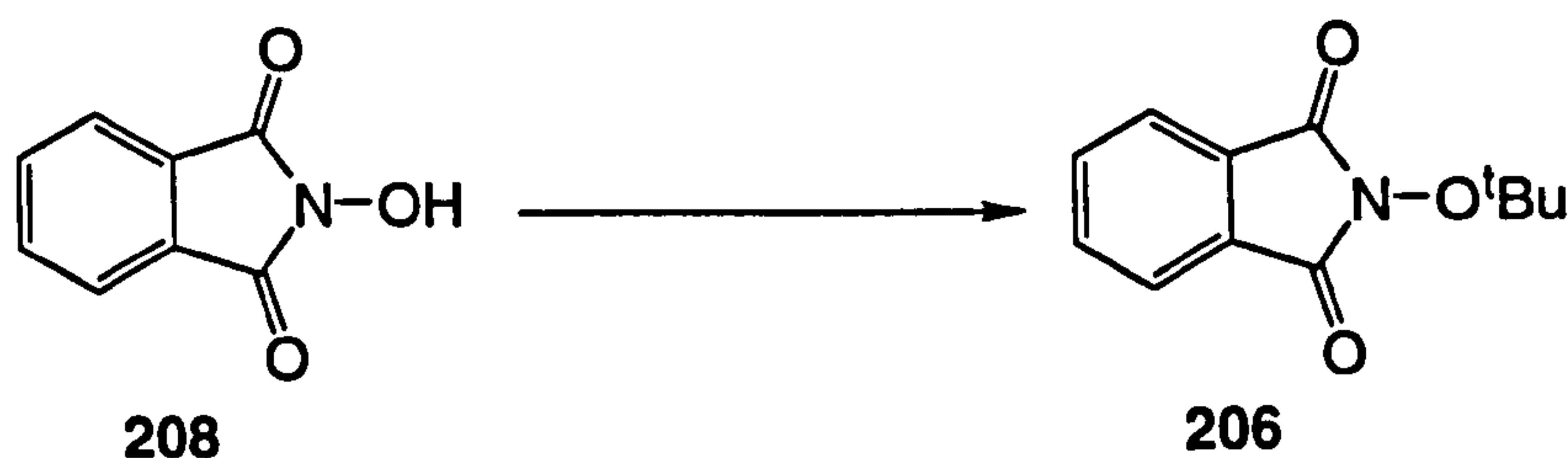
tert-Butyl acetate



According to the published method,²⁵⁴ dry distilled *tert*-butanol (294cm³, 3.07moles) and *N,N*-dimethylaniline (424cm³, 3.34mol) were dissolved in dry ether (400cm³) and heated to gentle reflux. This solution was treated with dry acetyl chloride (226cm³, 3.18moles) at a rate sufficient to maintain reflux (55°C) after removal of the heating. After addition of two-thirds of the acetyl chloride, precipitation of the amine hydrochloride salt began, along with vigorous reflux. The mixture was therefore cooled in an ice bath to halt the reflux, before addition of the remaining acetyl chloride. The resultant cloudy solution was refluxed for 1.5 h at which point two layers had developed. After cooling to 20°C, the solution was treated with water (400cm³) and the upper, organic layer removed. This ether solution was washed with aqueous sulphuric acid (10% w/v; 5 x 100cm³) before drying over MgSO₄ (24 h), filtration and evaporation of the solvent under reduced pressure. Distillation of the crude product gave the title compound as a clear mobile

liquid (189g, 51%), bp 95-95°C (lit.,²⁵⁴ 96-98°C); ν_{\max} (film) /cm⁻¹ 2981, 2935, 1739, 1457, 1368, 1256, 1174, 1020, 944, 843, 611; δ_{H} (CDCl₃; 400MHz) 1.44 (s, 9H, C(CH₃)₃), 1.98 (s, 3H, CH₃CO₂C(CH₃)₃); δ_{C} (CDCl₃; 100MHz) 28.1 (C(CH₃)₃), 80.2 (C(CH₃)₃), 170.6 (C=O); m/z 117 (MH⁺, 66%), 57 (100%), 43 (62%).

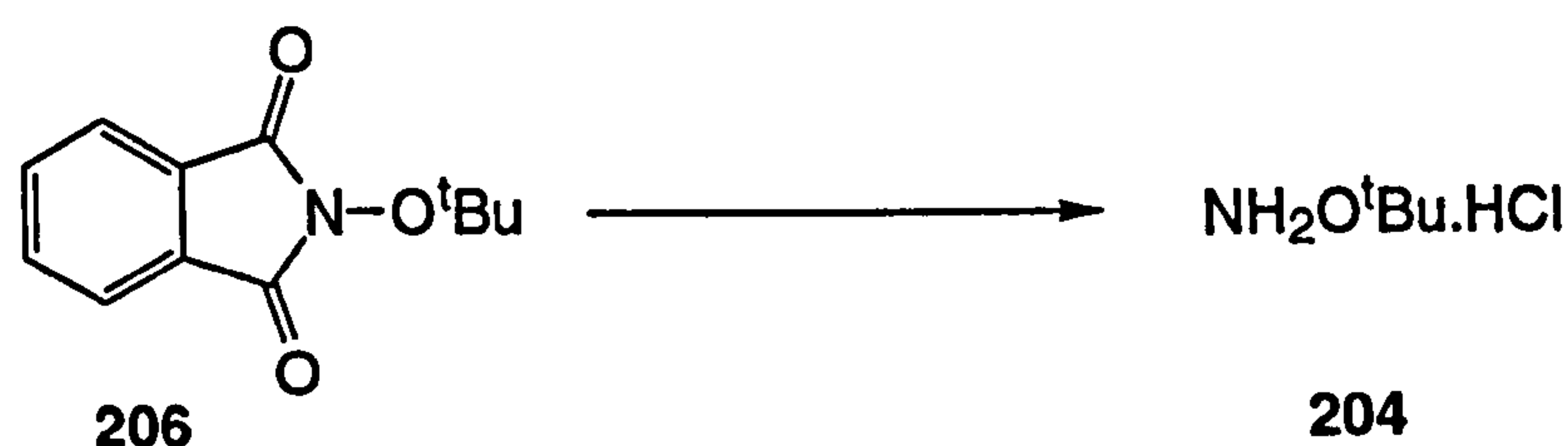
N-*tert*-Butoxyphthalimide (206)



The title compound **206** was prepared using a method based on that of Chimiak & Kolasa.^{252,253} A solution of N-hydroxyphthalimide **205** (328g, 2.01moles) in 1,4-dioxane (1300cm³) and 60% perchloric acid (20cm³) was treated with *tert*-butyl acetate (1085cm³, 8.05mol) and stirred at room temperature for 72 h. The solution was brought to pH9 with saturated aqueous sodium bicarbonate and extracted with chloroform (3 x 500cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure. The residue was then crushed and triturated with hexane (2 x 50cm³) to yield the title compound **206** as a white crystalline solid (437g, 99%), mp 110-111°C (lit.,²⁵³ 110-111°C) (Found: C, 65.80; H, 5.98; N, 6.39%; C₁₂H₁₃NO₃ requires C, 65.74; H, 5.98; N, 6.39%); ν_{\max} (KBr) /cm⁻¹ 2976, 2935, 1789, 1734, 1466, 1371, 1352, 1189, 1172, 1111, 1079, 970, 880, 703; δ_{H} (CDCl₃; 400MHz) 1.42 (s, 9H, C(CH₃)₃), 7.77 & 7.87 (m, 4H, Ar-H); δ_{C} (CDCl₃; 100MHz) 27.3 (C(CH₃)₃), 86.6 (C(CH₃)₃), 123.4 &

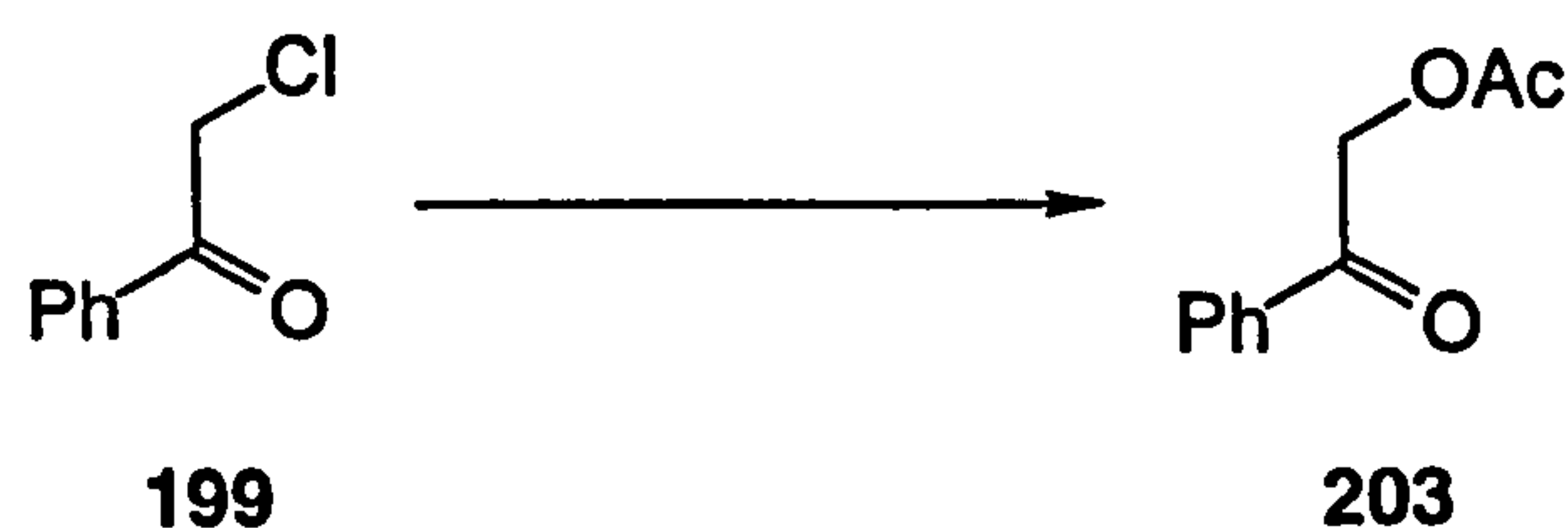
129.3 (Ar-CH), 134.4 (Ar-C), 165.7 (C=O); m/z 219 (M^+ , 3%), 204 (4%), 186 (3%), 164 (37%), 163 (33%), 104 (18%), 90 (13%), 76 (22%), 57 (100%).

O-*tert*-Butylhydroxylamine hydrochloride (204)



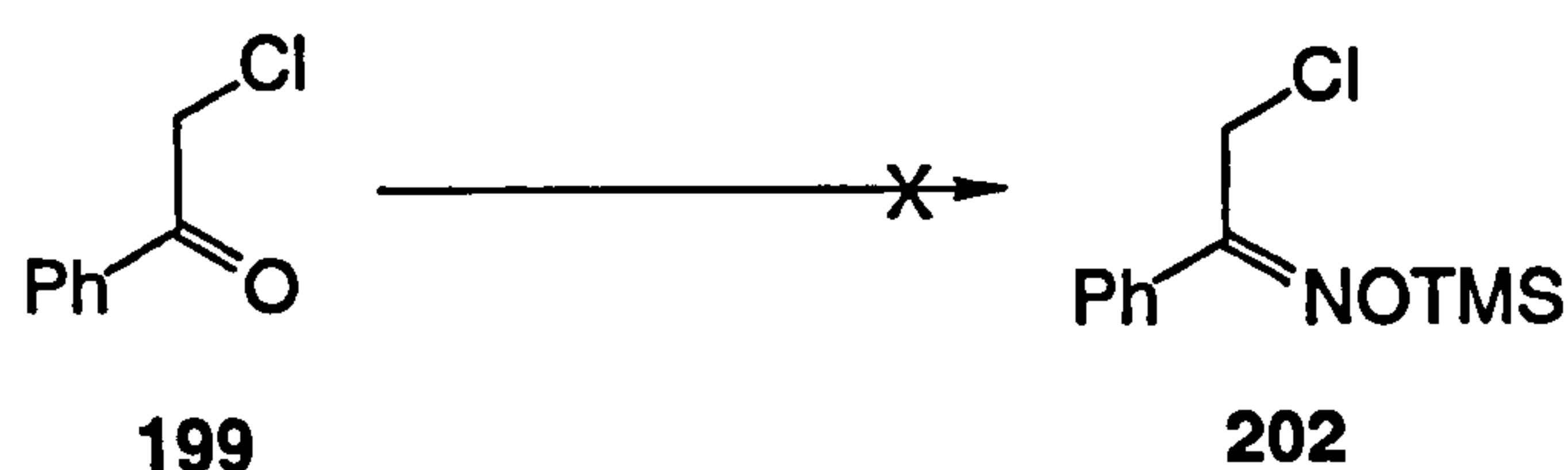
By the method of Chimiak & Kolasa^{252,253} a solution of N-*tert*-butoxyphthalimide (5.00g, 22.8mmol) in ethanol (50cm³) was treated with hydrazine hydrate (1.10cm³, 22.9mmol) in water (5cm³) to yield the title compound **204** as white amorphous solid (2.20g, 77%), mp 150-152°C (lit.²⁵³, 151-2°C); ν_{max} (KBr) /cm⁻¹ 3100-2800, 2691, 1575, 1529, 1380, 1169, 985, 828, 717; δ_{H} (CDCl₃; 400MHz) 1.45 (s, 9H, C(CH₃)₃), 10.56 (br s, 3H, NH₃⁺); δ_{C} (CDCl₃; 100MHz) 26.3 (C(CH₃)₃), 83.6 (C(CH₃)₃).

Benzoylmethyl acetate (203)



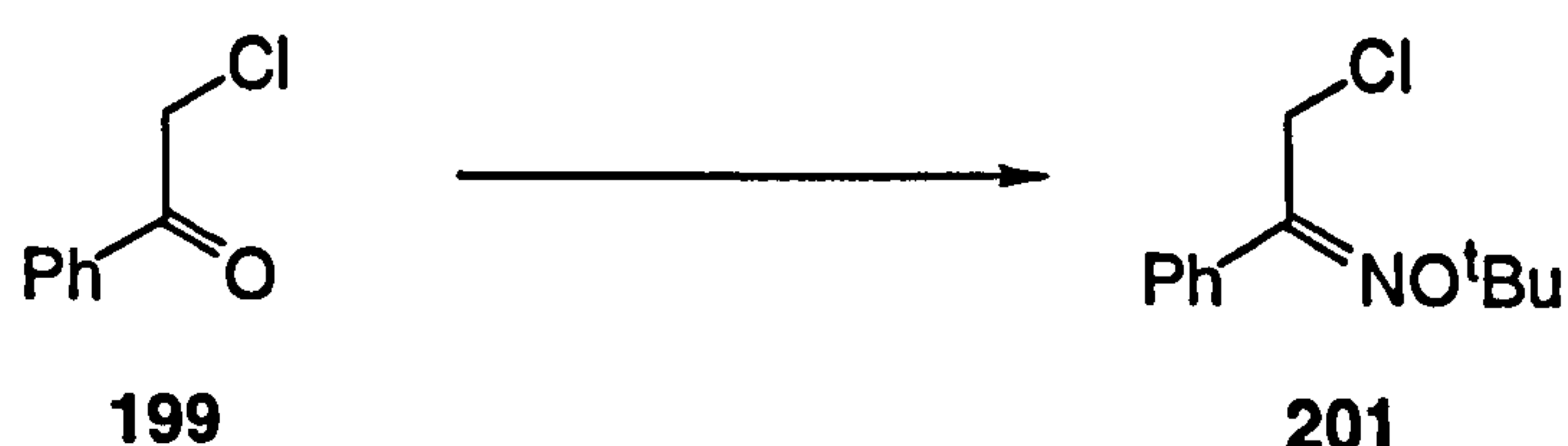
A solution of 2-chloroacetophenone **199** (1.00g, 6.47mmol) and sodium acetate (1.06g, 12.98mmol) in methanol (50cm³) was heated to reflux for 18 h and stirred at 20°C for 72 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound **203** as a colourless oil (150mg, 13%); ν_{\max} (film) /cm⁻¹ 3065, 2939, 1752, 1704, 1451, 1375, 1282, 1221, 757, 690; δ_{H} (CDCl₃; 400MHz) 2.23 (s, 3H, CH₃CO₂), 5.35 (s, 2H, PhCOCH₂OAc), 7.47 (m, 2H) & 7.65 (m, 3H) & 7.93 (m, 2H, Ar-H); δ_{C} (CDCl₃; 100MHz) 20.6 (CH₃CO₂), 66.0 (PhCOCH₂OAc), 127.8, 128.7 & 133.9 (Ar-CH), 134.2 (Ar-C), 170.5 (CH₃CO₂), 192.2 (PhC=O); m/z 179 (MH⁺, 5%), 105 (100%), 91 (12%), 77 (60%), 50 (36%), 43 (52%).

Attempted preparation of 2-chloroacetophenone O-trimethylsilyloxime (202)



By the method of Denmark and Dappen,²⁴⁹ a solution of 2-chloroacetophenone **199** (0.15g, 0.951mmol) in dry DCM (2cm³) with 4Å molecular sieves (0.5g) under an atmosphere of nitrogen was treated with O-trimethylsilylhydroxylamine (0.233cm³, 1.90mmol). After stirring at ambient temperature for 36 h, the solution was filtered and the solvent removed under reduced pressure but the residue contained none of the desired material **202**.

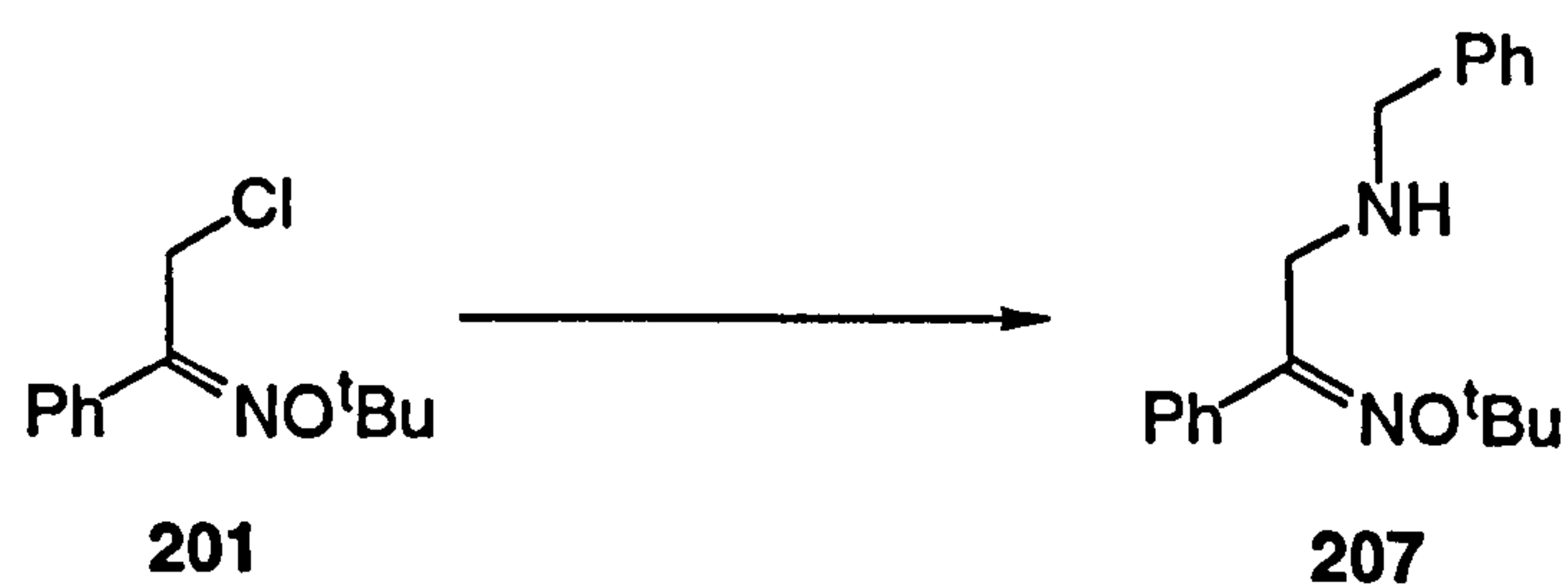
2-Chloroacetophenone O-*tert*-butyloxime (201)



A solution of 2-chloroacetophenone **199** (3.47g, 22.4mmol) in methanol (45cm³) was treated with O-*tert*-butylhydroxylamine hydrochloride (3.10g, 24.7mmol) and sodium acetate (2.03g, 24.7mmol) at 20°C. After 90 min, the solvent was evaporated under reduced pressure and the residue partitioned between DCM and water (30cm³ each). The aqueous phase was extracted with further DCM (2 x 30cm³) and the combined organic extracts were

dried over Na_2SO_4 , filtered and evaporated under reduced pressure to yield the *title compound 201* as a clear oil (4.69g, 93%) containing a mixture of geometric isomers (major:minor isomer = 11:1) (Found: M^+ 225.0920. $\text{C}_{12}\text{H}_{16}\text{NOCl}$ requires M^+ 225.0920); ν_{max} (film) $/\text{cm}^{-1}$ 2979, 1446, 1365, 1262, 1192, 977, 918, 776, 692; δ_{H} (CDCl_3 ; 400MHz) major isomer: 1.39 (s, 9H, $\text{C}(\text{CH}_3)_3$), 4.55 (s, 2H, CH_2Cl), 7.38 (m, 3H) & 7.74 (m, 2H, Ar-H); minor isomer: 1.31 (s, 9H, $\text{C}(\text{CH}_3)_3$), 4.48 (s, 2H, CH_2Cl), 7.38 (m, 3H) & 7.72 (m, 2H, Ar-H); δ_{C} (CDCl_3 ; 100MHz) major isomer: 27.6 ($\text{C}(\text{CH}_3)_3$), 32.5 (CH_2Cl), 80.3 ($\text{C}(\text{CH}_3)_3$), 125.9, 128.5 & 129.2 (Ar-CH), 134.3 (Ar-C), 150.7 ($\text{PhC}=\text{N}$); m/z 227 (^{37}Cl M^+ , 2%), 226 (2%), 225 (^{35}Cl M^+ , 7%), 172 (3%), 171 (5%), 170 (11%), 169 (13%), 134 (1%), 77 (15%), 57 (100%).

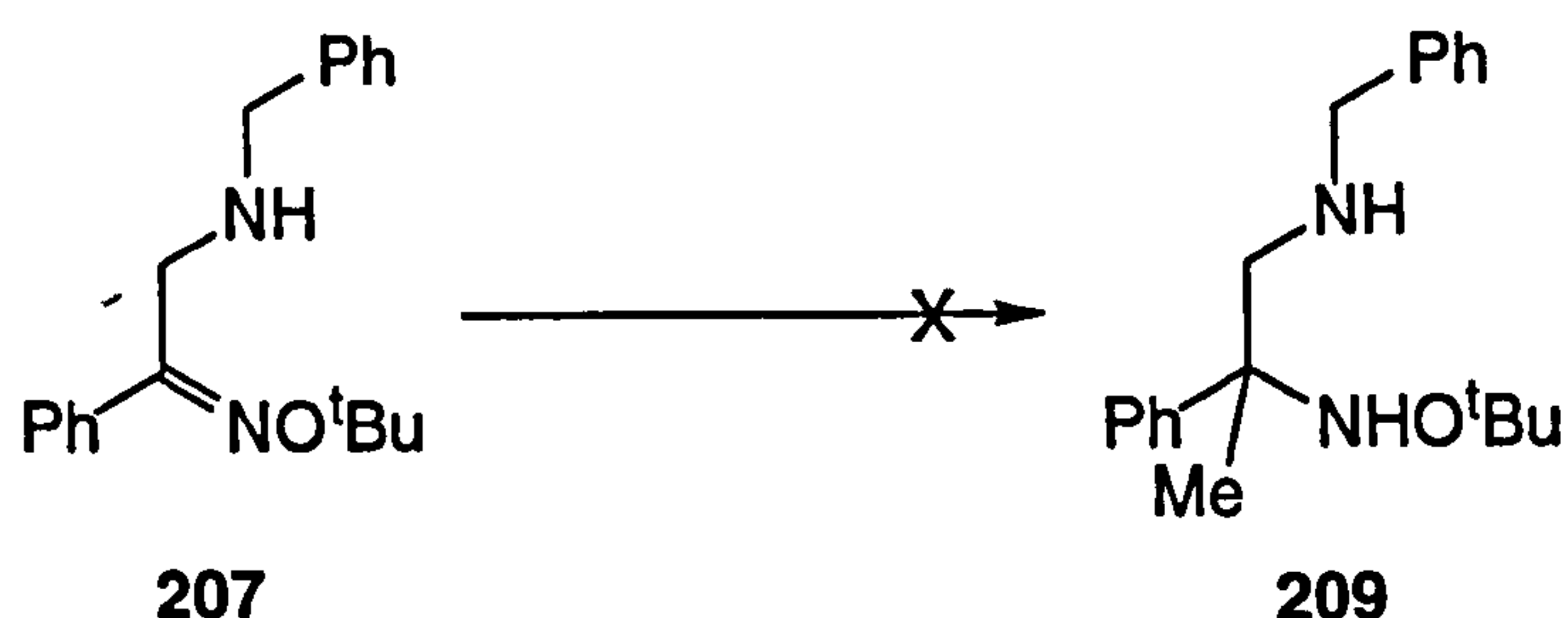
2-(N-Benzylamino)acetophenone O-*tert*-butyloxime (207)



A solution of 2-chloroacetophenone O-*tert*-butyloxime **201** (4.69g, 20.8mmol) in DMF (50cm³) was treated with benzylamine (6.81cm³, 62.3mmol) and stirred for 18 h. The solvent was removed under reduced pressure, the residue partitioned between DCM and water (100cm³ each) and the aqueous layer further extracted with DCM (2 x 100cm³). The combined organic extracts were dried over Na_2SO_4 , filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2 , hexane:EtOAc 9:1 v/v)

to yield the *title compound 207* as a colourless oil containing a mixture of geometric isomers (11.62g, 94%, major:minor isomer = 7.5:1) from which a pure sample of the major isomer was isolated by further careful chromatography (Found: C, 76.88; H, 8.28; N, 9.40%; MH^+ 297.1967. $C_{19}H_{24}N_2O$ requires C, 76.99; H, 8.16 ; N, 9.45%; MH^+ 297.1967); ν_{max} (film) $/cm^{-1}$ major isomer: 3062, 3027, 2976, 2929, 1496, 1455, 1364, 1192, 955, 916, 769, 739, 696; 1:1 mixed isomers: 3062, 3028, 2976, 2929, 1495, 1364, 1193, 948, 739, 696; δ_H ($CDCl_3$; 400MHz) major isomer: 1.36 (s, 9H, $C(CH_3)_3$), 2.06 (br s, 1H, NH), 3.77 (s, 2H, $NHCH_2Ph$), 3.85 (s, 2H, $PhCCH_2N$), 7.26-7.38 (m, 8H, Ar-H), 7.68 (m, 2H, Ar-H); minor isomer: 1.35 (s, 9H, $C(CH_3)_3$), 1.80 (br s, 1H, NH), 3.70 (s, 2H, $NHCH_2Ph$), 3.82 (s, 2H, $PhCCH_2N$), 7.26-7.38 (m, 8H, Ar-H), 7.58 (m, 2H, Ar-H); δ_C ($CDCl_3$; 100MHz) major isomer: 27.7 ($C(CH_3)_3$), 43.9 ($PhCCH_2N$), 53.2 ($NHCH_2Ph$), 79.4 ($C(CH_3)_3$), 126.3, 127.1, 128.2, 128.4, 128.5 & 128.8 (Ar-CH), 136.1 & 139.7 (Ar-C), 154.6 ($PhC=NO^tBu$); m/z 297 (MH^+ , 1%), 239 (1%), 223 (23%), 120 (52%), 106 (9%), 91 (100%).

Attempted preparation of N-benzyl-2-*tert*-butyloxyamino-2-phenylpropyl-amine (209)



A solution of 2-(N-benzylamino)acetophenone *O-tert*-butyloxime **207** (0.100g, 0.337mmol) in dry distilled THF (2cm³) under nitrogen was cooled to -75°C and treated with methyl lithium (1M solution in THF, 0.760cm³, 0.760mmol) dropwise over 1 min. The solution was stirred at -75°C for 2 h and warmed to 20°C overnight. The solution was quenched with water (10cm³), extracted with ether (3 x 20cm³) and the combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure. The residue did not yield the title compound **209** after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v).

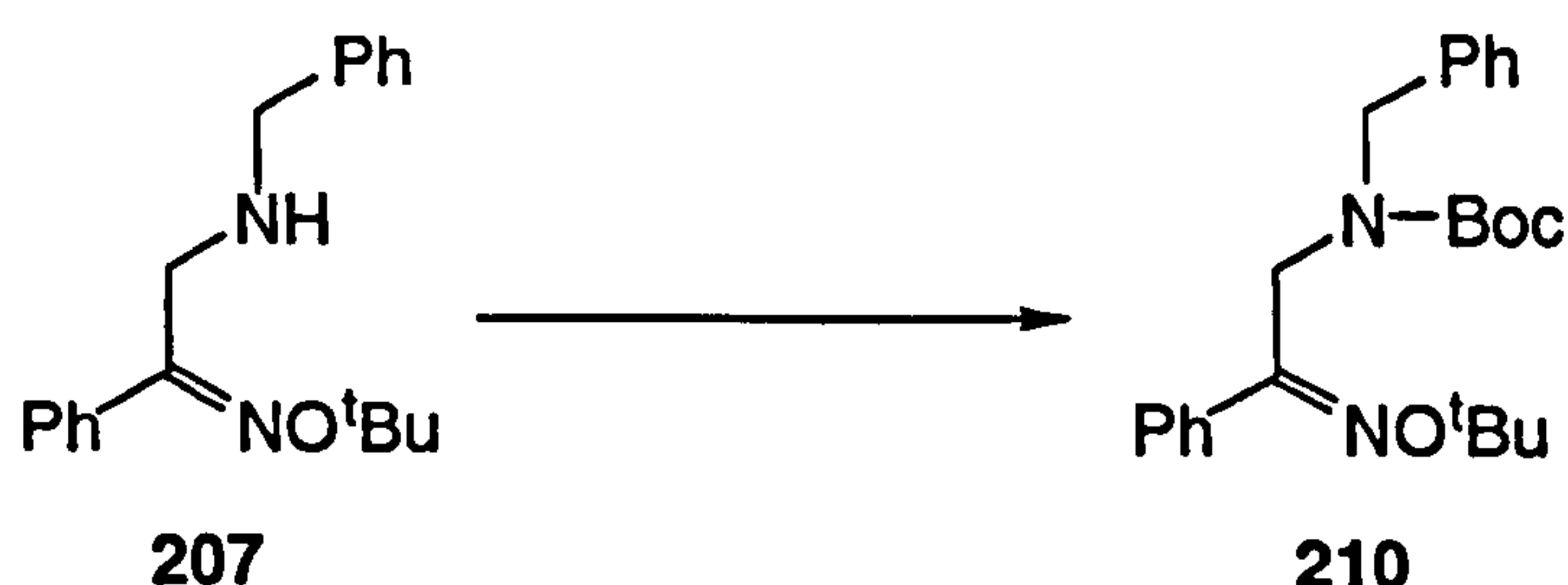
In a similar experiment, 2-(N-benzylamino)acetophenone *O-tert*-butyloxime **207** (0.100g, 0.337mmol) in dry distilled THF solution (2cm³) was treated with boron trifluoride etherate (93.0μl, 0.734mmol) and, after 10 min, with methyl lithium (1M solution in THF, 0.760cm³, 0.760mmol). Treatment was otherwise as above and did not yield the desired product.

A solution of 2-(N-benzylamino)acetophenone *O-tert*-butyloxime **207** (0.100g, 0.337mmol) in anhydrous ether (2cm³) under nitrogen was cooled to 0°C and treated with methylmagnesium bromide (3M solution in ether, 0.340cm³, 1.02mmol). After 2 h at 0°C,

the solution was allowed to reach 20°C overnight and otherwise treated as above. The residue yielded none of the desired, returning only unreacted starting material.

Similarly, a solution of 2-(N-benzylamino)acetophenone *O-tert*-butyloxime **207** (0.100g, 0.337mmol) in dry ether (2cm³) under nitrogen was cooled to 0°C and treated with boron trifluoride etherate (1.02cm³, 7.97mmol) and, after 20 min, with methylmagnesium bromide (3M solution in ether, 0.340cm³, 1.02mmol). This solution was treated otherwise as described above to afford only unchanged starting material.

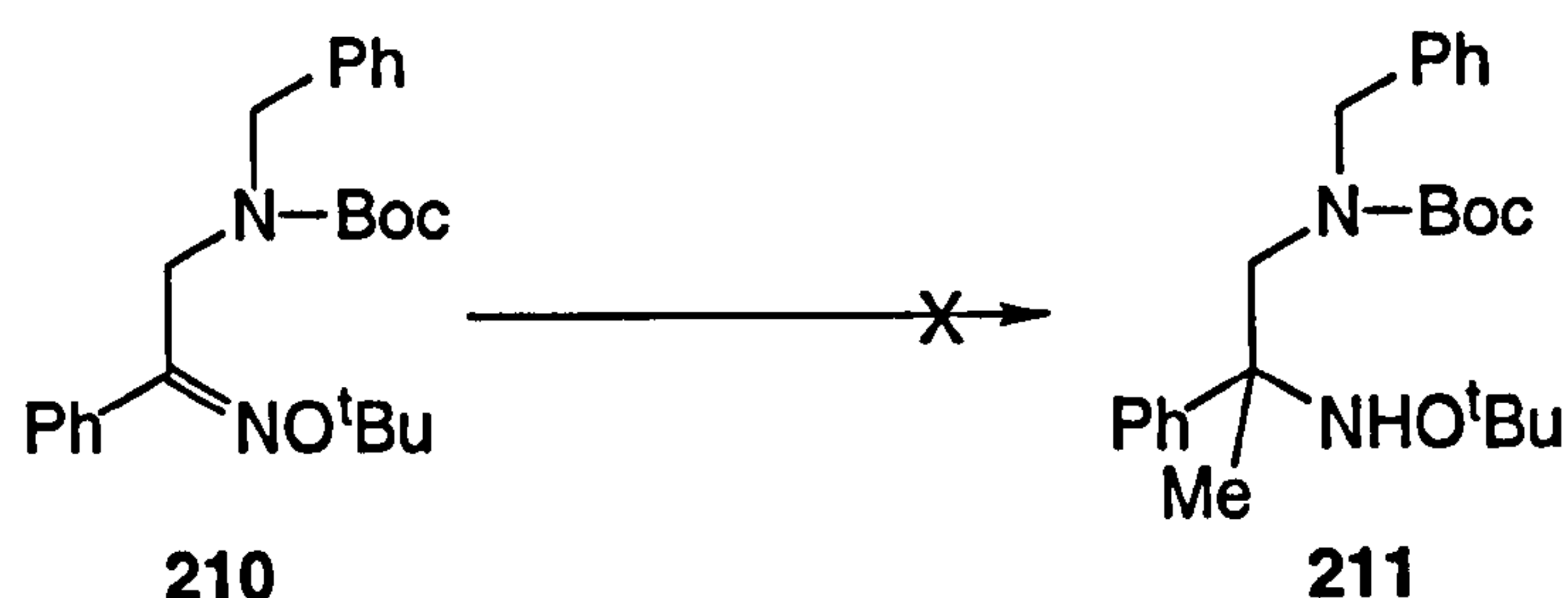
**2-(N-Benzyl-N-*tert*-butoxycarbonyl)aminoacetophenone *O-tert*-butyloxime
(210)**



A solution of 2-(N-benzylamino)acetophenone *O-tert*-butyloxime **207** (1.00g, 3.37mmol) in DCM (5cm³) at 0°C was treated with triethylamine (0.470cm³, 3.37mmol) and then a solution of di-*tert*-butyl dicarbonate (0.740g, 3.39mmol) in DCM (5cm³). After 1.5 h at 0°C the solution was washed with aqueous citric acid (1M; 5 x 20cm³), dried over MgSO₄, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to afford the title compound **210** as a white solid (1.10g, 2.77mmol, 82%) containing a mixture of carbamate rotamers (1.96:1) and oxime geometric isomers (5:1). VT ¹H NMR spectroscopy at 110°C in a mixture of CDCl₃,

and d_6 -DMSO showed collapse of the doubling of the two benzylic signals of the rotamers to confirm the presence of two compounds (*E* and *Z*-oxime isomers) each bearing a pair of *tert*-butyl signals, mp 107-111°C (Found: C, 71.70; H, 8.08; N, 6.95%; MH^+ 397.2484. $C_{24}H_{32}N_2O_3 + 0.25 H_2O$ requires C, 71.88; H, 8.11; N, 6.99%; MH^+ 397.2491); ν_{max} (KBr) / cm^{-1} 2977, 1691, 1417, 1365, 1244, 1191, 1166, 1118, 979, 938, 699; δ_H ($CDCl_3$; 400MHz, 20°C) 1.29, 1.38-1.45 & 1.52 (m, 18H, $NOC(CH_3)_3$ & $COC(CH_3)_3$ of major & minor oxime isomers), 4.11 (s, 1.3H), 4.22 (s, 0.7H), 4.56 (s, 0.3H), 4.73 (s, 1.7H, $PhCCH_2N$ & $NHCH_2Ph$ of major isomer), 4.19, 4.32, 4.34 & 4.47 (each s, 1H, $PhCCH_2N$ & $NHCH_2Ph$ of minor isomer), 7.17-7.78 (m, 10H, Ar-H of major and minor isomers); δ_C ($CDCl_3$, 100MHz, 20°C) major isomer: 27.4 & 28.3 ($NOC(CH_3)_3$ & $COC(CH_3)_3$), 39.2 & 40.6 ($PhCCH_2NBoc$), 49.1 ($N(Boc)CH_2Ph$), 79.4 & 80.1 ($NOC(CH_3)_3$ & $COC(CH_3)_3$), 126.7, 127.0, 127.6, 127.8, 128.1, 128.4 & 128.8, (Ar-C), 134.8 & 138.0 (Ar-C), 153.2 & 155.6 ($PhC=NO$ & $O=COC(CH_3)_3$); δ_H ($CDCl_3$ + d_6 -DMSO, 1:1 (v/v); 400MHz, 110°C) major isomer 1.28 & 1.37 (each s, 9H, $NOC(CH_3)_3$ & $COC(CH_3)_3$), 4.21 & 4.56 (each s, 2H, $PhCCH_2N$ & NCH_2Ph), 7.13-7.33 & 7.57 (m, 10H, Ar-H); δ_H ($CDCl_3$ + d_6 -DMSO, 1:1 (v/v); 400MHz, 110°C) minor isomer 1.25 & 1.36 (each s, 9H, $NOC(CH_3)_3$ & $COC(CH_3)_3$), 4.22 & 4.37 (each s, 2H, $PhCCH_2N$ & NCH_2Ph), 7.13-7.33 & 7.57 (Ar-H); m/z 397 (MH^+ , 0.2%), 341 (1%), 297 (1%), 241 (1%), 185 (5%), 61 (100%), 57 (20%), 43 (85%).

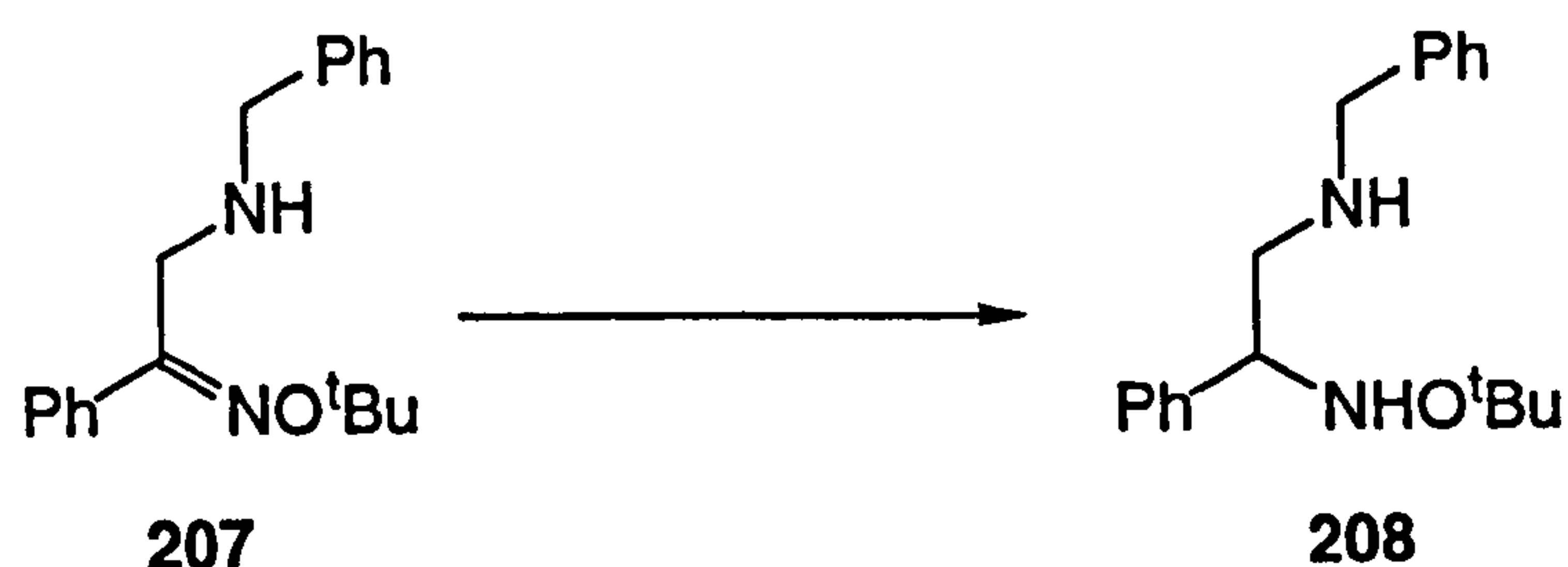
Attempted preparation of N-benzyl-N-*tert*-butoxycarbonyl-2-*tert*-butyloxyamino-2-phenylpropylamine (211)



A solution of 2-(N-benzyl-N-*tert*-butoxycarbonyl)aminoacetophenone *O-tert*-butyloxime **210** (0.100g, 0.252mmol) in anhydrous toluene (2cm³) under an atmosphere of nitrogen was cooled to -75°C and treated with methyl lithium (1.6M solution in toluene, 473μl, 0.756mmol) over 10 min. No reaction was observed by TLC analysis after 2 h, nor after warming to 20°C over 18 h. The reaction was quenched with water (2cm³) and the solution extracted with toluene (3 x 10cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure to return only unreacted starting material (83%).

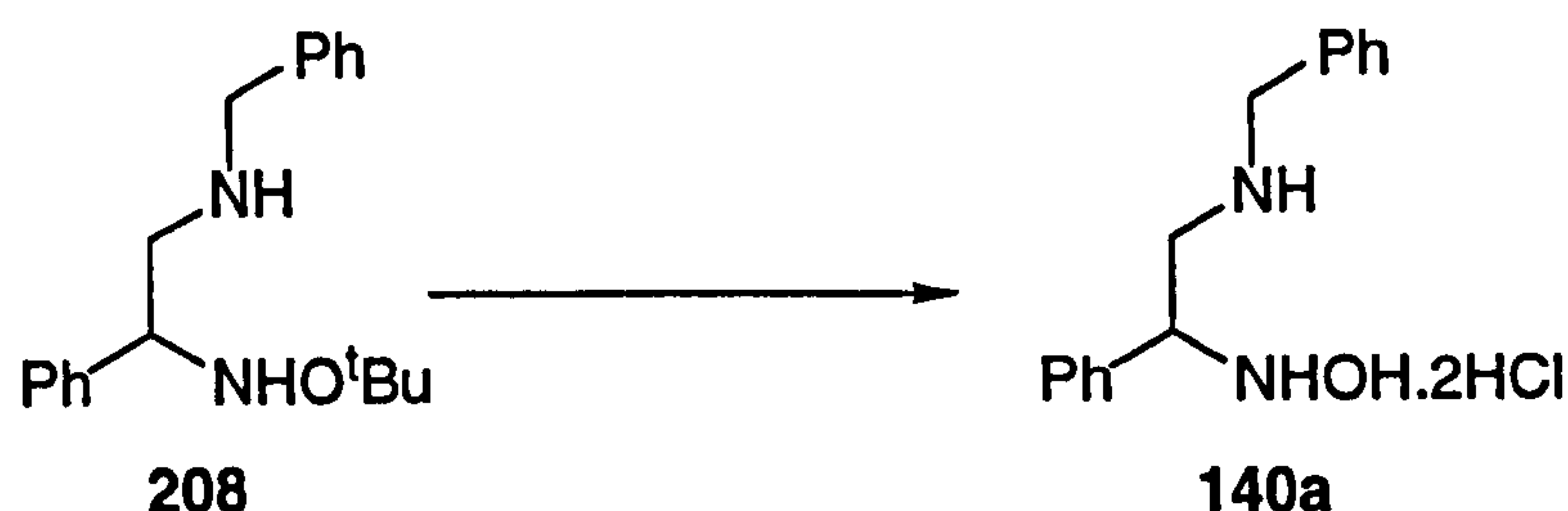
This experiment was repeated as above with the slight modification of addition of boron trifluoride etherate (93.0μl, 0.734mmol) at -75°C and stirring for 10 min prior to addition of the methyllithium. After identical treatment thereafter, the residue was purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to afford none of the desired material **211**. The isolated products were the starting oxime **210** (6.0mg, 6%) and the deprotected oxime **207** (35.0mg, 47%).

N-Benzyl-2-*tert*-butyloxyamino-2-phenylethylamine (208)



A solution of 2-(N-benzylamino)acetophenone O-*tert*-butyloxime **207** (0.500g, 1.69mmol) in dry THF (10cm³) at 0°C was treated with borane-THF complex (1M solution in THF, 6.74cm³, 6.74mmol) under a nitrogen atmosphere. After warming to 20°C for 1 h, the solution was cooled to 0°C and treated dropwise with aqueous HCl (6M; 10cm³), keeping the temperature below 5°C. After 30 min, this solution was warmed to 20°C and stirred for a further 30 min, before basifying with aqueous NaOH (2M) and extraction with ether (3 x 50cm³). The combined organic extracts were dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to yield the *title compound* **208** as a clear oil (0.500g, 92%). (Found: C, 76.10; H, 8.82; N, 9.09%; M⁺ 299.2123. C₁₉H₂₆N₂O requires C, 76.47; H, 8.78 ; N, 9.38%; MH⁺ 299.2123); ν_{\max} (film) /cm⁻¹ 3086, 3063, 3029, 2974, 2929, 2870, 1495, 1455, 1361, 1242, 1196, 755, 700; δ_{H} (CDCl₃; 400MHz) 1.11 (C(CH₃)₃), 2.89 (dd, 2H, *J* 5.4, 12.2Hz, PhCHCHHN), 3.01 (dd, 1H, *J* 8.0, 12.2Hz, PhCHCHHN), 3.81 (s, 2H, NHCH₂Ph), 4.09 (dd, 1H, *J* 5.4, 8.0Hz, PhCHNO), 7.26-7.36 (Ar-H); δ_{C} (CDCl₃; 100MHz) 26.8 (C(CH₃)₃), 52.4 (PhCHCH₂N), 53.7 (NHCH₂Ph), 65.0 (PhCHNO), 76.6 (C(CH₃)₃), 126.8, 127.4, 128.0, 128.2 & 128.3 (Ar-CH), 140.1 & 140.7 (Ar-C); *m/z* 299 (MH⁺, 94%), 243 (7%), 225 (1%), 210 (24%), 122 (37%), 121 (14%), 120 (100%), 106 (57%), 91 (78%).

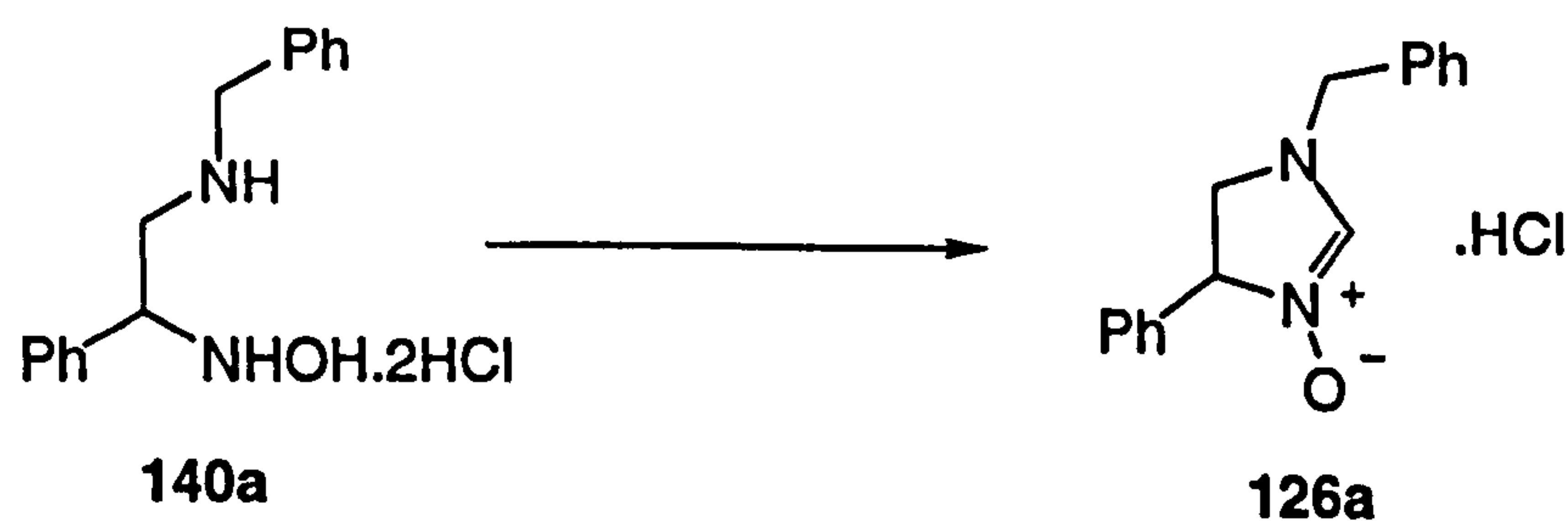
N-Benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride (140a)



A solution of N-benzyl-2-*tert*-butyloxyamino-2-phenylethylamine **208** (33.3g, 112mmol) in methanol (150cm³) was treated dropwise with conc. sulphuric acid (150cm³) with stirring as the temperature rose to approximately 70°C. The resultant solution was cooled to 20°C and basified with ice cold NaOH solution (2M). The solution was extracted with ether (3 x 250cm³) and the combined organic extracts dried over MgSO₄ and filtered. Dry gaseous HCl was bubbled through the resultant solution for 1 h before evaporation of the solvent under reduced pressure. The residue was dried thoroughly under high vacuum before trituration with DCM to yield the *title compound* **140a** as an amorphous white solid (24.1g, 76.4mmol, 68%) (Found: C, 57.10; H, 6.41; N, 8.77%; M⁺ 243.1490. C₁₅H₂₀N₂OCl₂ requires C, 57.15; H, 6.40; N, 8.89%; M⁺ 243.1497); ν_{\max} (KBr) /cm⁻¹ 3400-2200, 1572, 1499, 1458, 1426, 994, 753, 697; δ_{H} (D₂O, internal standard TSP-d₄; 400MHz) 3.68 (dd, 1H, *J* 7.3, 13.4Hz, PhCHCHHN), 3.89 (dd, 1H, *J* 6.2, 13.4Hz, PhCHCHHN), 4.33 (s, 2H, NHCH₂Ph), 4.77 (dd, 1H, *J* 7.3, 6.2Hz, PhCHNH₂OH), 7.45-7.60 (m, 10H, Ar-H); δ_{C} (D₂O; TSP-d₄; 100MHz) 49.1, 54.6 & 64.5 (PhCHCH₂N, NHCH₂Ph & PhCHNH₂OH) 131.6, 132.3, 132.6, 132.7, 132.9, 133.0 & 134.0 (Ar-C & Ar-CH); *m/z* FAB⁺ 243 (MH⁺, 19%), 210 (20%), 105 (57%), 91 (56%), 61 (96%), 45 (100%).

In a separate experiment, a solution of N-benzyl-2-*tert*-butoxyamino-2-phenylethylamine **208** (0.800g, 2.68mmol) in methanol (10cm³) was treated with conc. hydrochloric acid (10cm³) and heated to reflux for 18 h. The solution was cooled to 20°C then basified with aqueous NaOH (2M) and extracted with EtOAc (3 x 30cm³). The combined organic extracts were separated and dried (Na₂SO₄) before evaporation under reduced pressure. The residue was treated with HCl (1M solution in anhydrous ether, 10cm³) to afford a sticky brown solid (containing 29% of the desired product **140a** by reverse phase HPLC analysis). Repeated trituration with cold DCM gave an off-white solid (0.480g, 1.52mmol, 57%) (93% purity by HPLC) consistent with the desired material **140a** by ¹H NMR spectroscopy (D₂O).

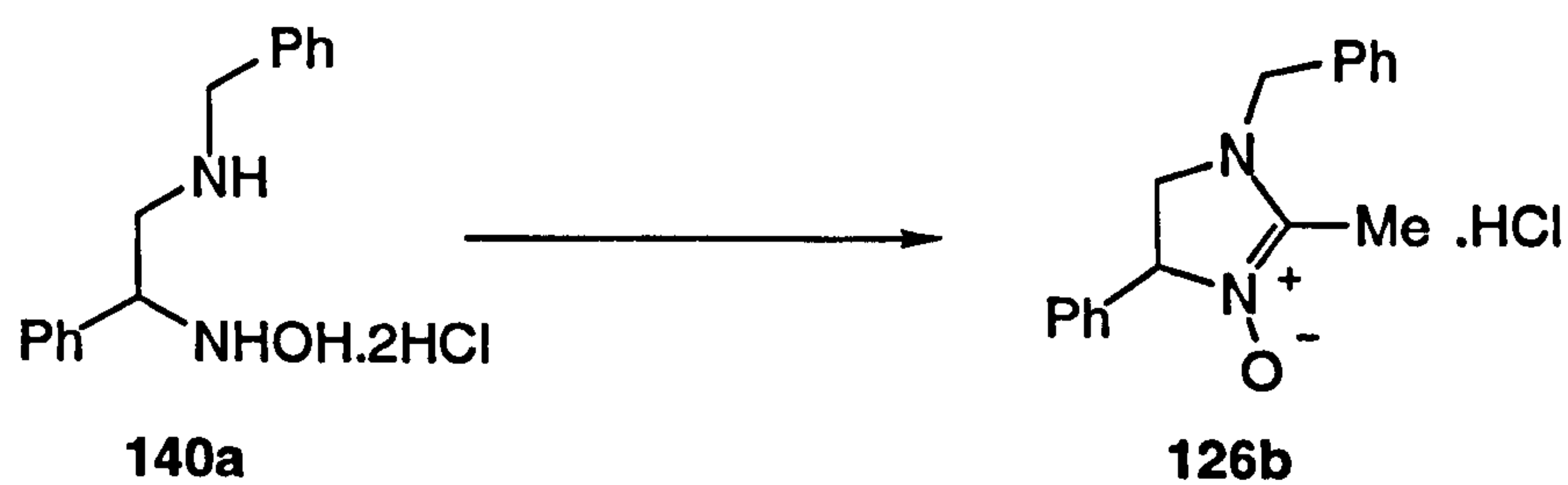
3-Benzyl-5-phenyl-4,5-dihydroimidazole-1-oxide hydrochloride (**126a**)



A solution of N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.360g, 1.14mmol) in dry toluene (6cm³) was treated with triethyl orthoformate (435μl, 2.62mmol) under a nitrogen atmosphere. After warming to 60°C for 1 h, the solvent was evaporated under reduced pressure and the residue dried thoroughly under high vacuum to yield the *title compound* **126a** as an unstable colourless film (0.329g, 100%); (M⁺-Cl 253.1337. C₁₆H₁₆N₂O requires M⁺-Cl 253.1341); δ_H (CDCl₃; 400MHz) 3.52 & 4.17 (each

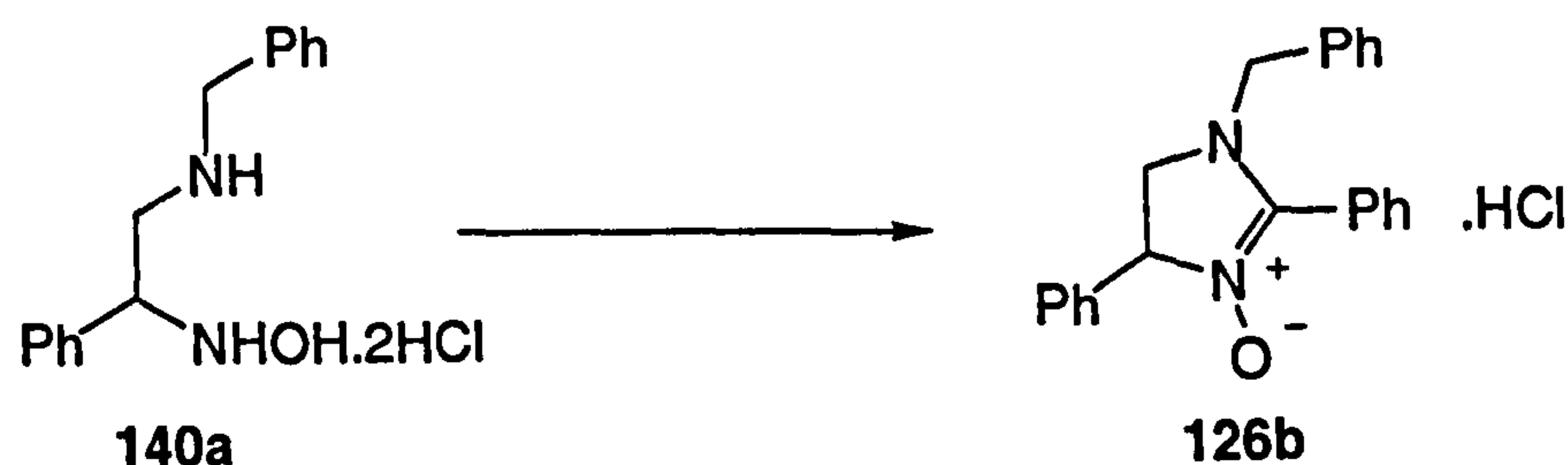
t, 1H, *J* 12.3Hz, PhCHCH₂N), 4.80 (s, 2H, NCH₂Ph), 5.50 (t, 1H, *J* 12.3Hz, PhCHNO), 7.31-7.42 (m, 10H, Ar-H), 9.67 (s, 1H, N=CH-N) δ_c (CDCl₃; 100MHz) 52.8, 55.5 (NCH₂Ph & PhCHCH₂N), 67.6 (PhCHNO), 127.4, 128.9, 129.0, 129.3, 129.4 & 129.6 (Ar-CH) 132.0 & 134.4 (Ar-C), 157.3 (N=CH-N) ; *m/z* 254 (MH⁺, 1%), 85 (60%), 83 (100%), 61 (30%), 47 (44%).

3-Benzyl-2-methyl-5-phenyl-4,5-dihydroimidazole-1-oxide hydrochloride (126b)



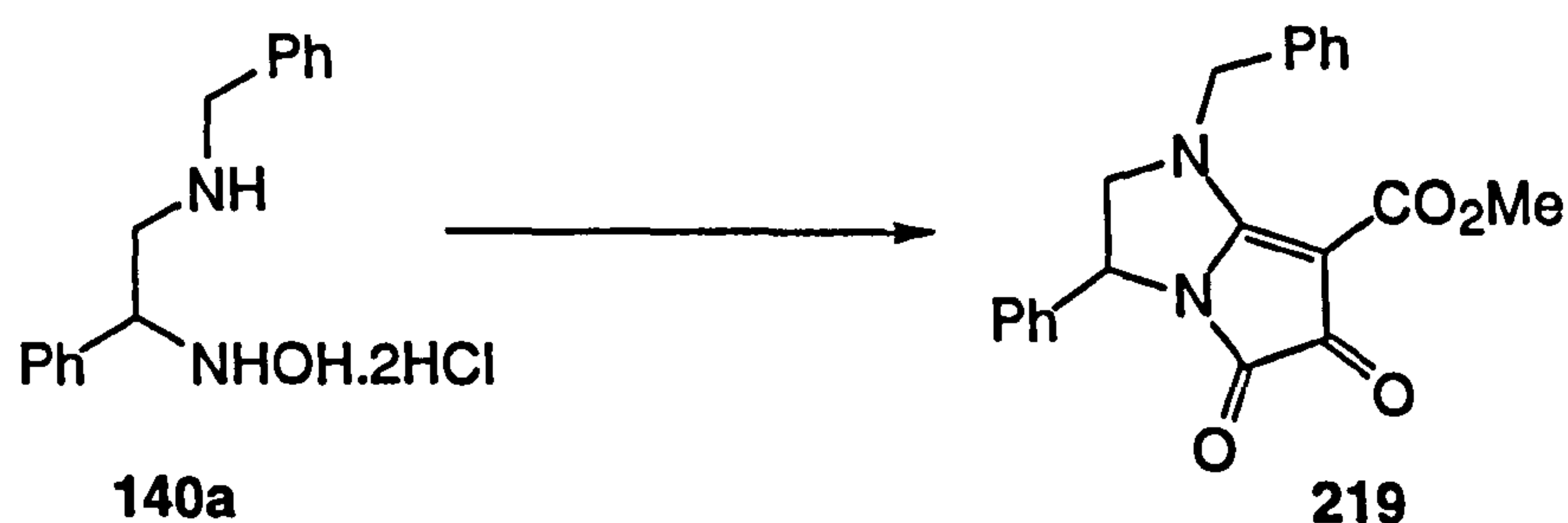
Prepared as for the 2-H nitrone 126a, from N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (80.0mg, 0.254mmol) and triethyl orthoacetate (58.0 μ l, 0.317mmol) in dry DCM (1cm³) to give the title compound 126b as colourless gum (78.0mg, 100%) with 97% purity by HPLC (M⁺-Cl 266.1416. C₁₇H₁₈N₂O requires M⁺-Cl 266.1419); ν_{\max} (film) /cm⁻¹ 3450-2400, 1613, 1456, 1261, 1030, 758, 731, 701; δ_H (CDCl₃; 400MHz) 2.65 (s, 3H, N=CCH₃), 3.51 & 4.14 (each t, 1H, *J* 10.2Hz, PhCHCH₂N), 4.63 (s, 2H, NCH₂Ph), 5.52 (t, 1H, *J* 10.2Hz, PhCHCH₂N), 7.15-7.45 (Ar-H); δ_c (CDCl₃; 100MHz) 11.7 (N=C(CH₃)-N), 51.4 & 55.0 (PhCHCH₂N & NCH₂Ph), 66.4 (PhCHCH₂N), 127.1, 127.8, 129.4, 129.5 & 129.7 (Ar-CH), 132.3 & 134.7 (Ar-C), 167.6 (N=C(CH₃)-N); *m/z* 267 (MH⁺, 13%), 251 (3%), 91 (71%), 61 (100%), 43 (82%).

3-Benzyl-2,5-diphenyl-4,5-dihydroimidazole-1-oxide hydrochloride (126c)



Prepared as for the 2-H nitrone 126a from N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.100g, 0.317mmol) and triethyl orthobenzoate (90.0μl, 0.400mmol) in dry DCM (2cm³) to give a mixture containing the *title compound* 126c by APCI⁺ MS; *m/z* 329 (MH⁺, 10%), 313 (M⁺-O, 100%).

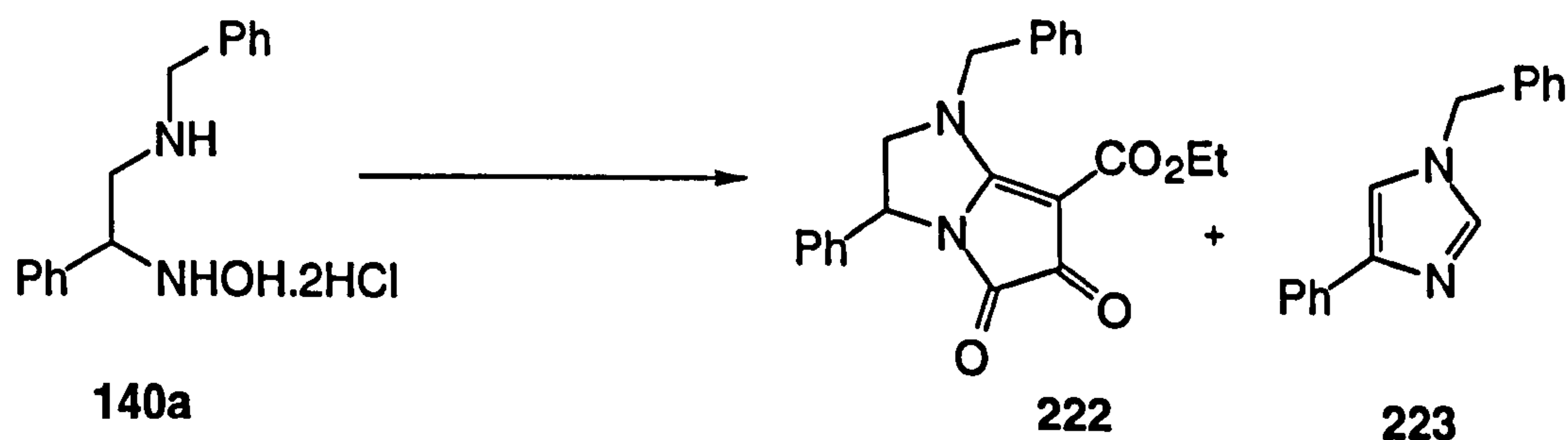
1-Benzyl-7-methoxycarbonyl-3-phenyl-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-*a*]imidazole-5,6-dione (219)



A slurry of N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol) in anhydrous DCM (2cm³) at 30°C under an atmosphere of nitrogen was treated with triethyl orthoformate (131μl, 0.793mmol) and stirred for 1.5 h after which time the slurry had become a clear solution. The mixture was then treated with triethylamine

(176 μ l, 1.26mmol) and dimethyl acetylenedicarboxylate (97.0 μ l, 0.793mmol) and stirred at 30°C for 18 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the *title compound 219* as a brown film (133mg, 58%) (M^+ 362.1266. C₂₁H₁₈N₂O₄ requires M^+ 362.1266); ν_{\max} (KBr) /cm⁻¹ 3030, 2950, 1756, 1677, 1605, 1471, 1347, 1237, 1114, 752, 706; δ_H (CDCl₃; 300MHz) 3.77 (dd, 1H, J 5.0, 11.6Hz, PhCHCHHN, 3.86 (s, 3H, CO₂CH₃), 4.36 (dd, 1H, J 9.4, 11.6Hz, PhCHCHHN), 5.28 (dd, 1H, J 5.0, 9.4Hz, PhCHCH₂N), 5.55 (s, 2H, NCH₂Ph), 7.12 & 7.26-7.42 (m, 10H, Ar-H); δ_C (CDCl₃; 100MHz) 51.5 (CO₂CH₃), 52.5 (NCH₂Ph), 54.9 (PhCHCH₂N), 62.1 (PhCHCH₂N), 86.8 (CCO₂CH₃), 125.9, 128.6, 128.9, 129.2, 129.3 & 129.4 (Ar-CH), 133.8 & 136.4 (Ar-C), 157.7, 163.5, 165.9 & 177.0 (NC=CCO₂CH₃, NC=O, CO₂CH₃ & NC(=O)C=O); m/z 362 (M^+ , <1%), 330 (2%), 303 (1%), 157 (2%), 91 (41%), 84 (27%) 44 (58%), 28 (100%).

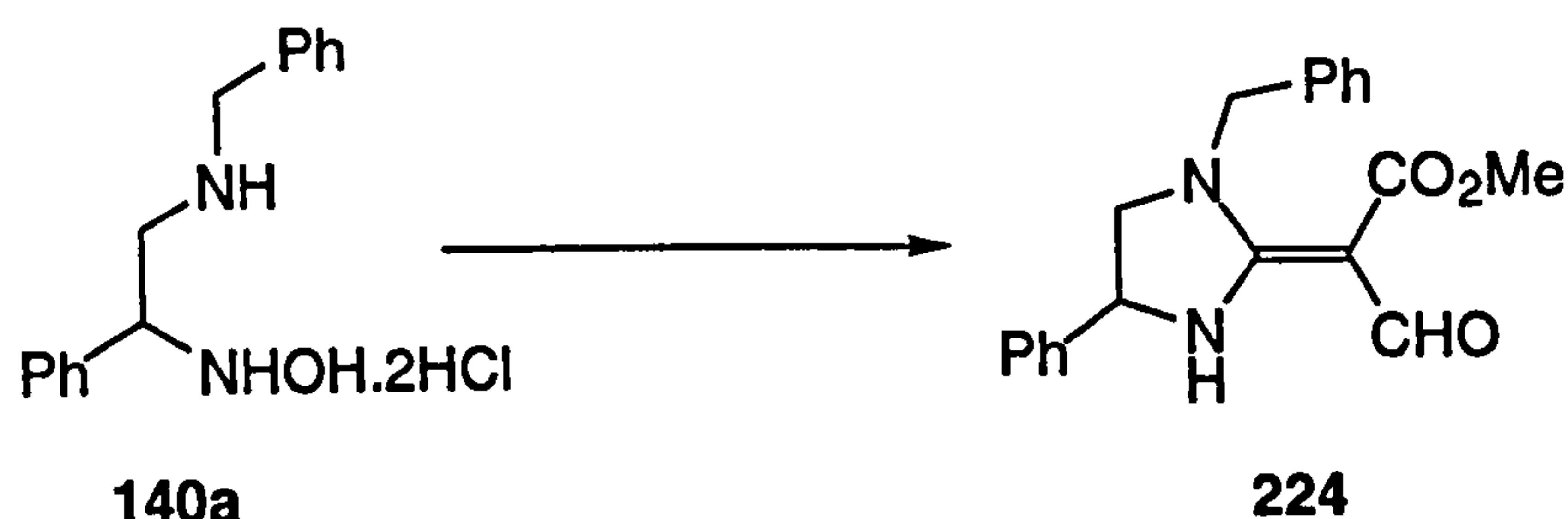
1-Benzyl-7-ethoxycarbonyl-3-phenyl-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-*a*]imidazole-5,6-dione (222)



Prepared as for dimethyl acetylenedicarboxylate cycloadduct **219** using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.300g, 0.952mmol), triethylorthoformate (198 μ l, 1.19mmol), triethylamine (264 μ l, 1.89mmol) and diethyl

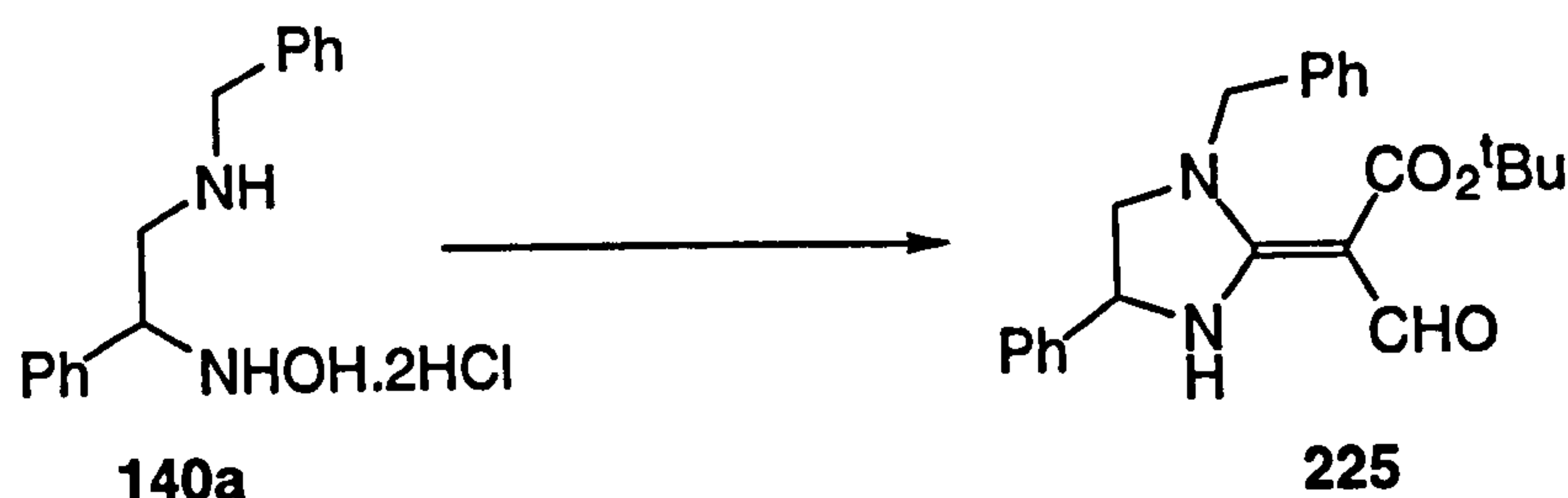
acetylene dicarboxylate (190 μ l, 1.19mmol) and DCM (3cm³) at 45°C. The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 1:1 v/v) to afford 1-benzyl-4-phenylimidazole **223** as a white crystalline solid (83.0mg, 37% based on **140a**) and the title compound **222** as a yellow gum (72.0mg, 20%); **222**: (Found MH⁺ 377.1498. C₂₂H₂₀N₂O₄ requires MH⁺ 377.1501); δ_{H} (CDCl₃; 400MHz) 1.36 (t, 3H, *J* 7.0Hz, OCH₂CH₃), 3.75 (dd, 1H, *J* 4.8, 11.2Hz, PhCHCHHN), 4.37 (m, 3H, PhCHCHHN & CO₂CH₂CH₃), 5.28 (dd, 1H, *J* 4.8, 9.2Hz, PhCHCH₂N), 5.44 & 5.59 (each d, 1H, *J* 14.8Hz, NCH₂Ph), 7.12 & 7.27-7.41 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 14.5 (OCH₂CH₃), 52.5 (NCH₂Ph), 54.9 (PhCHCH₂N), 60.3 (CO₂CH₂CH₃), 62.1 (PhCHCH₂N), 87.1 (C=CCO₂CH₂CH₃), 125.9, 128.5, 128.9, 129.2, 129.3 & 129.4 (Ar-CH), 133.9 & 136.4 (Ar-C), 157.7, 163.0, 165.9 & 177.1 (NC=CCO₂CH₂CH₃, NC=O, CO₂CH₂CH₃ & NC(=O)C=O); *m/z* 377 (MH⁺, 1%), 331 (11%), 303 (2%), 235 (2%), 105 (55%), 91 (100%); **1-Benzyl-4-phenyl-1H-imidazole 223**: (Found: C, 79.15; H, 6.07; N, 11.02%; M⁺ 234.1157. C₁₆H₁₄N₂ + 0.5 H₂O requires C, 78.98; H, 6.20; N, 11.51%; M⁺ 234.1157); δ_{H} (CDCl₃; 400MHz) 5.06 (s, 2H, NCH₂Ph), 7.16-7.38 (m, 9H, Ar-H & PhC=CHN), 7.56 (m, 1H, N=CH-N), 7.76 (m, 2H, Ar-H); δ_{C} (CDCl₃; 100MHz) 50.8 (NCH₂Ph), 115.0 (PhC=CHN), 124.6, 126.7, 127.2, 128.2, 128.4 & 128.9 (Ar-CH), 133.9 & 135.9 (Ar-C), 137.5 (N=CH-N), 142.4 (PhC=CHN); *m/z* 234 (M⁺, 23%), 91 (100%), 77 (15%).

1-Benzyl-2-(formylmethoxycarbonylmethylene)-4-phenyl-tetrahydroimidazole (224)



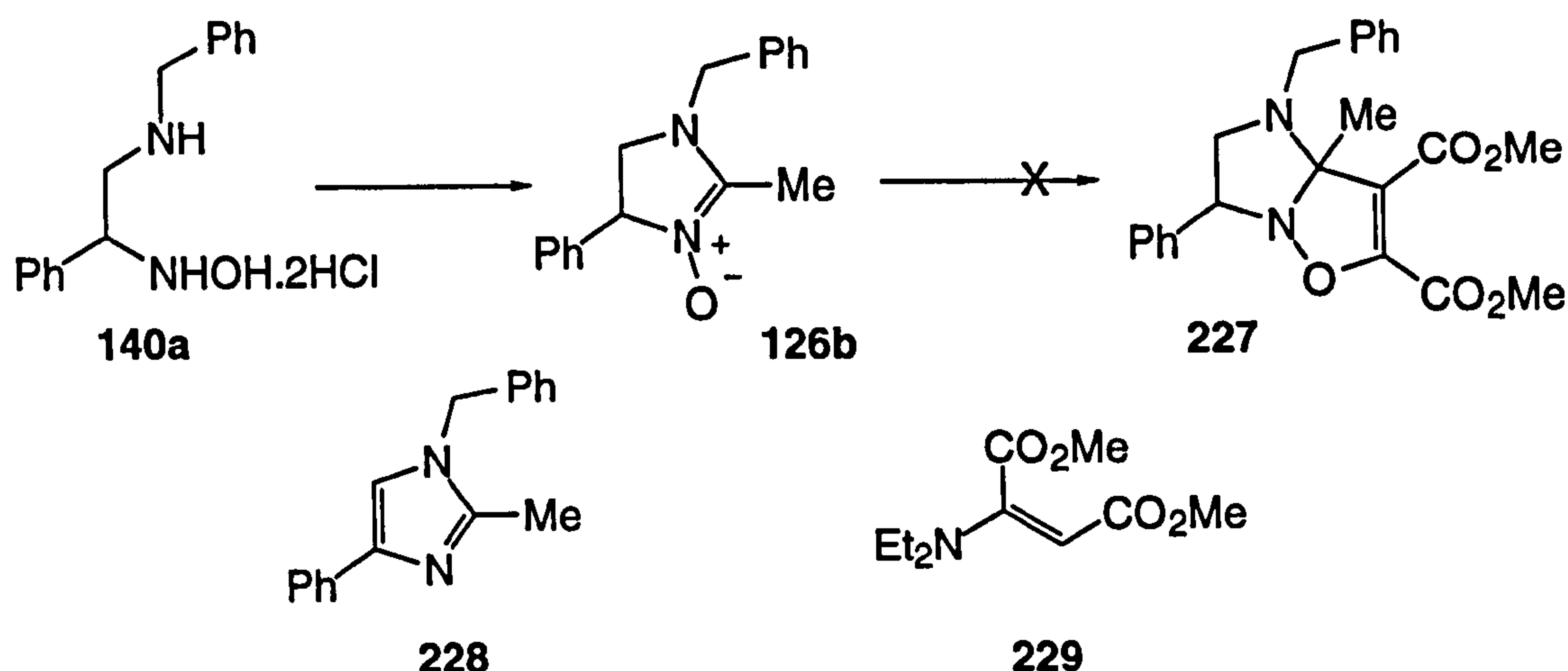
Prepared as for the dimethyl acetylenedicarboxylate cycloadduct **220**, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.200g, 0.634mmol), triethylorthoformate (132 μ l, 1.19mmol), triethylamine (177 μ l, 1.26mmol) and methyl propiolate (71.0 μ l, 0.793mmol) in toluene (3cm³) at 60°C. The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 1:1 v/v) to afford 1-benzyl-4-phenyl-1H-imidazole **223** as a white crystalline solid (9mg, 6%) and the *title compound* **224** as a pale yellow oil (78.0mg, 37%); (Found: C, 69.17; H, 6.02 ; N, 8.16%; M⁺ 336.1474. C₂₀H₂₀N₂O₃ + 0.5 H₂O requires C, 69.55; H, 6.12 ; N, 8.11%; M⁺ 366.1474); ν_{max} (film) /cm⁻¹ 3026, 1678, 1604, 1544, 1439, 1352, 1278, 1101; δ_{H} (CDCl₃; 400MHz) 3.32 (dd, 1H, *J* 7.3, 9.8Hz, PhCHCHHN), 3.69 (s, 3H, CO₂CH₃), 3.88 (t, 1H, *J* 9.8Hz, PhCHCHHN), 4.58 & 4.67 (each d, 1H, *J* 16.3Hz, NCH₂Ph), 4.99 (dd, 1H, *J* 7.3, 9.8Hz, PhCHCH₂N), 7.15-7.37 (m, 10H, Ar-H), 9.69 (s, 1H, CHO), 9.86 (br s, 1H, NH); δ_{C} (CDCl₃; 100MHz) 50.8 (CO₂CH₃), 53.3 (NCH₂Ph), 56.5 (PhCHCH₂N), 58.0 (PhCHCH₂N), 88.0 (C=CCO₂CH₃), 125.9, 128.1, 128.8, 128.9 & 129.1 (Ar-CH), 135.6 & 139.9 (Ar-C), 165.0 & 168.5 (NC=CCO₂CH₃ & CO₂CH₃), 186.7 (CHO) ; *m/z* 336 (M⁺, 14%), 276 (12%), 176 (31%), 175 (12%), 149 (12 %), 147 (11%), 111(13%), 105 (17%), 104 (41%), 97 (18%), 91 (100%).

1-Benzyl-2-(formyl-*tert*-butoxycarbonylmethylene)-4-phenyl-tetrahydroimidazole (225)



Prepared as for the dimethyl acetylenedicarboxylate cycloadduct **219**, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.200g, 0.634mmol), triethylorthoformate (132 μ l, 1.19mmol), triethylamine (186 μ l, 1.33mmol), *tert*-butyl propiolate (109 μ l, 0.793mmol) and toluene (3cm³) at 60°C. The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 1:1 v/v) to afford the 1-benzyl-4-phenyl-1*H*-imidazole **223** (67.0mg, 45%) and the *title compound* **225** as a pale yellow oil (108mg, 45%) (Found: MH⁺ 379.2022. C₂₃H₂₆N₂O₃ requires MH⁺ 379.2022); δ_{H} (CDCl₃; 400MHz) 1.51 (s, 9H, C(CH₃)₃), 3.32 (dd, 1H, *J* 8.5, 10.8Hz, PhCHCHHN), 3.82 (t, 1H, *J* 10.8Hz, PhCHCHHN), 4.60 & 4.68 (each d, 1H, *J* 15.4Hz, NCH₂Ph), 4.96 (dd, 1H, *J* 8.5, 10.8Hz, PhCHCH₂N); δ_{C} (CDCl₃; 100MHz) 28.6 (C(CH₃)₃), 53.0 (NCH₂Ph), 56.1 (PhCHCH₂N), 58.0 (PhCHCH₂N), 79.4 (C(CH₃)₃), 89.6 (CCO₂C(CH₃)₃), 126.0, 128.0, 128.3, 128.4, 128.6 & 128.7 (Ar-CH), 135.7 & 139.8 (Ar-C), 164.9 & 167.8 (CO₂C(CH₃)₃ & NC=CCO₂C(CH₃)₃), 186.7 (CHO); *m/z* 379 (MH⁺, 12%), 323 (22%), 305 (20%), 277 (6%), 215 (6%), 120 (7%), 117 (5%), 105 (15%), 104 (15%), 91 (100%), 57 (14%).

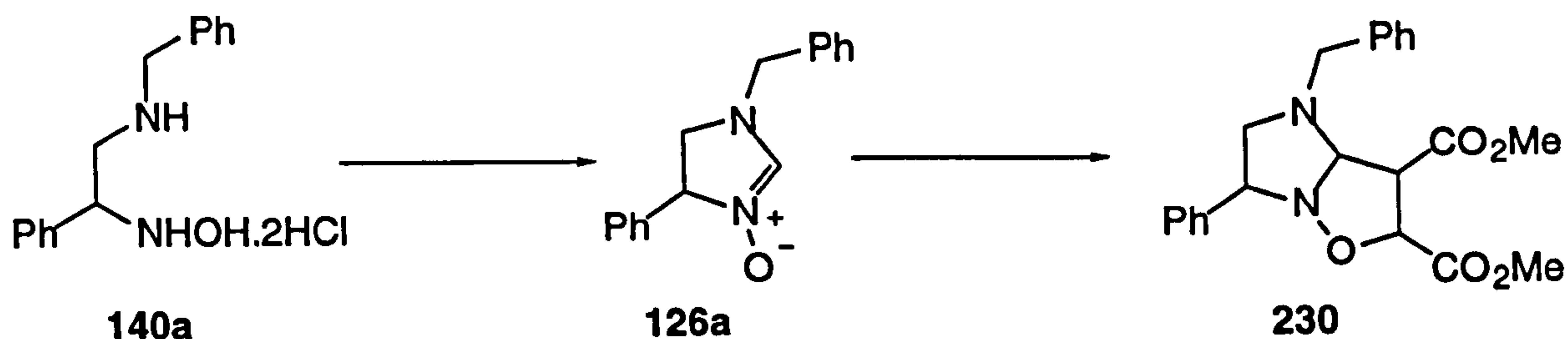
Attempted preparation of 1-benzyl-7a-methyl-6,7-dimethoxycarbonyl-3-phenyl-1,2,3,7a-tetrahydro-1*H*-imidazo[1,2-*b*]isoxazole (227)



A slurry of N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.100g, 0.317mmol) in anhydrous DCM (2cm³) under nitrogen was treated with triethyl orthoacetate (73.0μl, 0.398mmol) and warmed to 20°C for 18 h before addition of triethylamine (88.0μl, 0.632mmol) and then dimethyl acetylenedicarboxylate (49.0μl, 0.399mmol). After 18 h at 20°C, the solution was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) but none of the desired cycloadduct **227** was isolated. However, from this mixture it was possible to isolate and characterise 1-benzyl-2-methyl-4-phenyl-1*H*-imidazole **228** (31.0mg, 39% based on **140a**) and dimethyl 2-(diethylamino)but-2-enediolate **229** (24.0mg, 28% based on DMAD); **1-Benzyl-2-methyl-4-phenyl-1*H*-imidazole 228**: δ_H (CDCl₃; 250MHz) 2.39 (s, 3H, CH₃), 5.05 (s, 2H, NCH₂Ph), 7.09-7.37 & 7.75 (m, 11H, Ar-H & PhC=CHN); δ_C (CDCl₃; 63MHz) 12.8 (CH₃), 49.5 (NCH₂Ph) 115.3 (PhC=CHN), 124.2, 126.1, 126.3, 127.0, 128.0 & 128.7 (Ar-CH), 133.8 & 135.8 (Ar-C), 139.7 & 145.0 (PhC=CHN & N=CCH₃); APCI⁺ *m/z* 249 (MH⁺, 100%). **Dimethyl 2-**

(diethylamino)but-2-enedioate **229**: δ_{H} (CDCl_3 ; 400MHz) 1.18 (t, 6H, J 7.1Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.18 (q, 4H, J 7.1Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.63 & 3.93 (each s, 3H, CO_2CH_3), 4.61 (s, 1H, $\text{HCCCO}_2\text{CH}_3$); δ_{C} (CDCl_3 ; 100MHz) 12.4 ($\text{N}(\text{CH}_2\text{CH}_3)_2$), 44.6 ($\text{N}(\text{CH}_2\text{CH}_3)_2$), 50.4 & 52.6 (CO_2CH_3), 82.6 ($\text{HC}=\text{CCO}_2\text{CH}_3$), 153.5 ($\text{NC}=\text{CO}_2\text{CH}_3$), 165.9 & 168.0 (CO_2CH_3); APCI^+ m/z 216 (MH^+ , 100%).

1-Benzyl-6,7-dimethoxycarbonyl-3-phenylhexahydroimidazo[1,2-*b*]isoxazole (230)

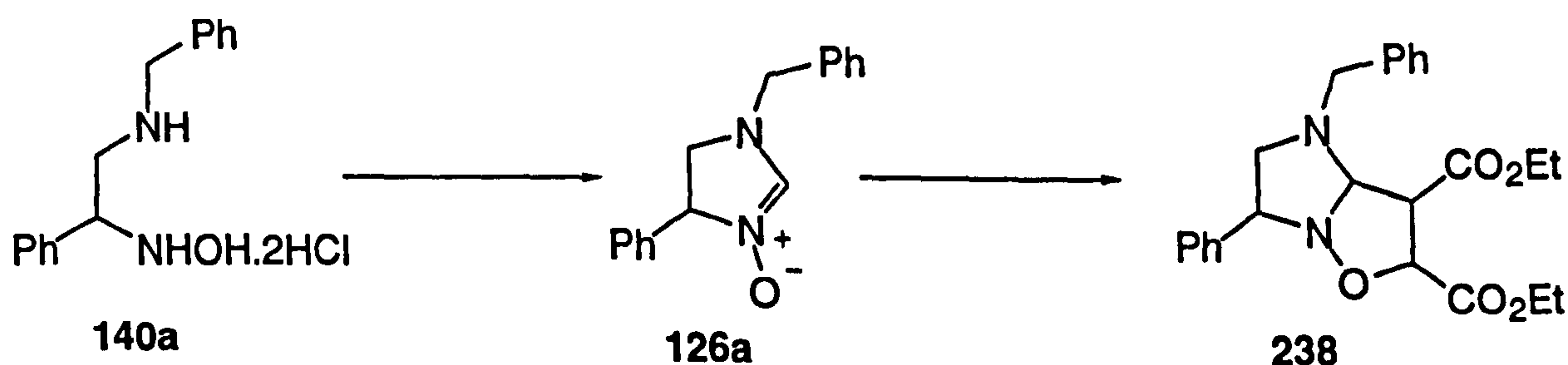


A slurry of N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.200g, 0.634mmol) in dry toluene (3cm³) under a nitrogen atmosphere was treated with triethylorthoformate (1.06cm³, 6.34mmol) and warmed to 60°C for 1 h. The resultant solution was then treated with triethylamine (186μl, 1.33mmol) and dimethyl maleate (99.0μl, 0.793mmol) and stirred at 60°C for 18 h. The solution was cooled to 20°C and treated with saturated aqueous sodium bicarbonate (10cm³) and extracted with DCM (3 x 30cm³). The combined organic extracts were dried over MgSO_4 , filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2 , hexane:EtOAc 4:1 v/v) to give the *title compound* **230** as a colourless oil (161mg, 64%).

Recrystallisation from methanol gave white needles for X-ray crystallographic analysis, mp

106-107°C (Found : C, 66.67; H, 6.09; N, 7.06%; M^+ 396.1685; $C_{22}H_{24}N_2O_5$ requires C, 66.65; H, 6.10; N, 7.06%; M^+ 396.1685); ν_{\max} (KBr) / cm^{-1} 3028, 2952, 2894, 2812, 1760, 1446, 1435, 1364, 1270, 1223, 1165, 1049, 757, 737, 699; δ_H ($CDCl_3$; 400MHz) 2.40 (dd, 1H, J 9.5, 10.8Hz, PhCHCHHN), 3.38 (dd, 1H, J 6.4, 9.5Hz, PhCHCHHN), 3.47 (d, 1H, J 5.8Hz, NCHCHCO₂Me), 3.58 (d, 1H, J 12.6Hz, NCHHPh), 3.70 & 3.77 (each s, 3H, CO₂CH₃), 3.93 (d, 1H, 12.6Hz, NCHHPh), 4.42 (dd, 1H, J 6.4, 10.8Hz, PhCHNO), 4.63 (s, 1H, NCHCHCO₂CH₃), 4.98 (d, 1H, J 5.8Hz, NOCHCO₂CH₃), 7.20-7.39 (Ar-H); δ_C ($CDCl_3$; 100MHz) 52.4 (2 x CO₂CH₃), 57.4 (NCHCHCO₂CH₃), 57.5 (NCH₂Ph), 58.6 (PhCHCH₂N), 69.2 (PhCHNO), 75.5 (NOCHCO₂CH₃), 87.6 (NCHCHCO₂CH₃), 126.9, 127.4, 127.6, 128.2, 128.5 & 128.9 (Ar-CH), 136.8 & 138.7 (Ar-C), 168.4 & 169.1 (2 x CO₂CH₃); m/z 397 (MH^+ , 4%), 381 (0.2%), 337 (0.3%), 253 (5%), 105 (100%), 91 (37%) 61 (49%), 45 (49%).

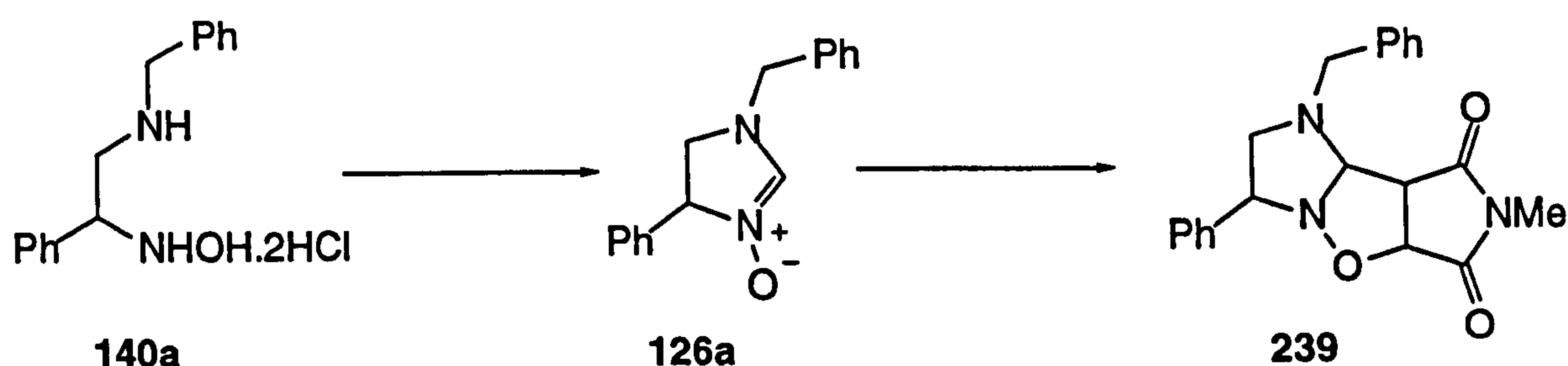
**1-Benzyl-6,7-diethoxycarbonyl-3-phenylhexahydro-1*H*-imidazo[1,2-
b]isoxazole (238)**



Prepared as for the dimethyl maleate cycloadduct 230 using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (2.00g, 6.34mmol), triethylorthoformate (1.32cm³, 7.93mmol), triethylamine (1.86cm³, 13.3mmol) and diethyl

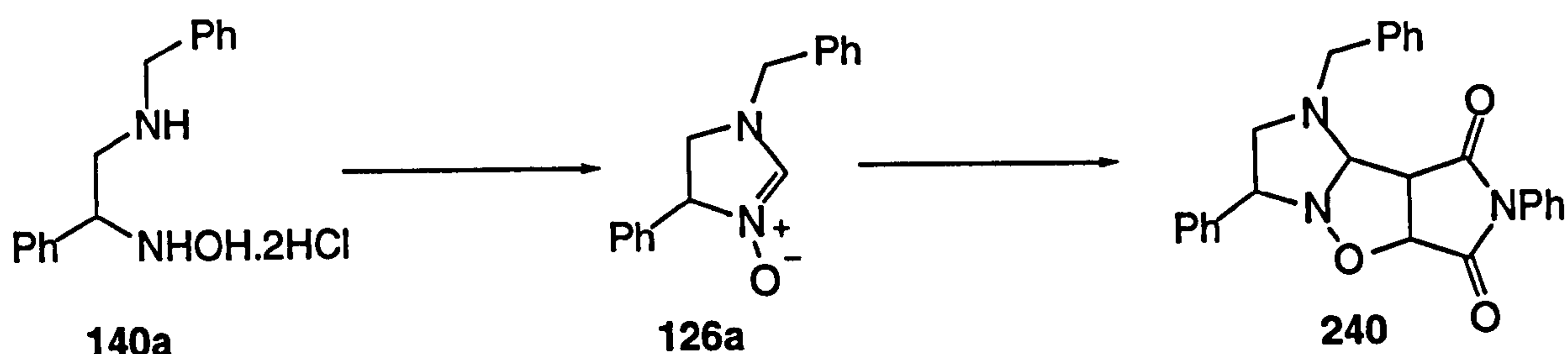
maleate (1.03cm³, 6.61mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the *title compound 238* as a pale yellow oil (966mg, 2.28mmol, 36%) (Found: C, 66.76; H, 6.96; N, 6.84%; MH⁺ 425.2076. C₂₄H₂₈N₂O₅ + 0.5 H₂O requires C, 66.49; H, 6.74; N, 6.46%; MH⁺ 425.2081); ν_{\max} (film) /cm⁻¹ 3062, 3030, 2982, 2934, 1737, 1276, 1206, 1044, 701; δ_{H} (CDCl₃; 400MHz) 1.26 (t, 3H, *J* 7.1Hz, CO₂CH₂CH₃), 1.30 (t, 3H, *J* 7.1Hz, CO₂CH₂CH₃), 2.40 (dd, 1H, *J* 9.5, 10.8Hz, PhCHCHHN), 3.36 (dd, 1H, *J* 6.4, 9.5Hz, PhCHCHHN), 3.45 (dd, 1H, *J* 1.1, 5.9Hz, NCHCHCO₂CH₂CH₃), 3.58 & 3.96 (each d, 1H, *J* 12.8Hz, NCH₂Ph), 4.20 & 4.24 (each m, 2H, 2 x CO₂CH₂CH₃), 4.42 (dd, 1H, *J* 6.4, 10.8Hz, PhCHCH₂N), 4.63 (s, 1H, NCHCHCO₂CH₂CH₃), 4.95 (d, 1H, *J* 5.9Hz, NOCHCO₂CH₂CH₃), 7.22-7.42 (m, 10, Ar-H); δ_{C} (CDCl₃; 100MHz) 14.1 (2 x CO₂CH₂CH₃), 57.5 (NCHCHCO₂CH₂CH₃ & NCH₂Ph), 58.7 (PhCHCH₂N), 61.5 (2 x CO₂CH₂CH₃), 69.2 (PhCHCH₂N), 75.6 (NOCHCO₂CH₂CH₃), 87.7 (NCHCHCO₂CH₂CH₃), 127.0, 127.4, 127.6, 128.3, 128.5 & 129.0 (Ar-CH), 137.0 & 139.0 (Ar-C), 168.0 & 168.8 (2 x CO₂CH₂CH₃); *m/z* 425 (MH⁺, 18%), 237 (17%), 235 (22%), 192 (78%), 190 (29%), 175 (82%), 173 (76%), 122 (23%), 120 (56%), 108 (62%), 106 (100%).

1-Benzyl-8-methyl-3-phenyloctahydro-8*H*-imidazo[1,2-*b*]pyrrolo[3,4-*d*]isoxazole-7,9-dione (239)



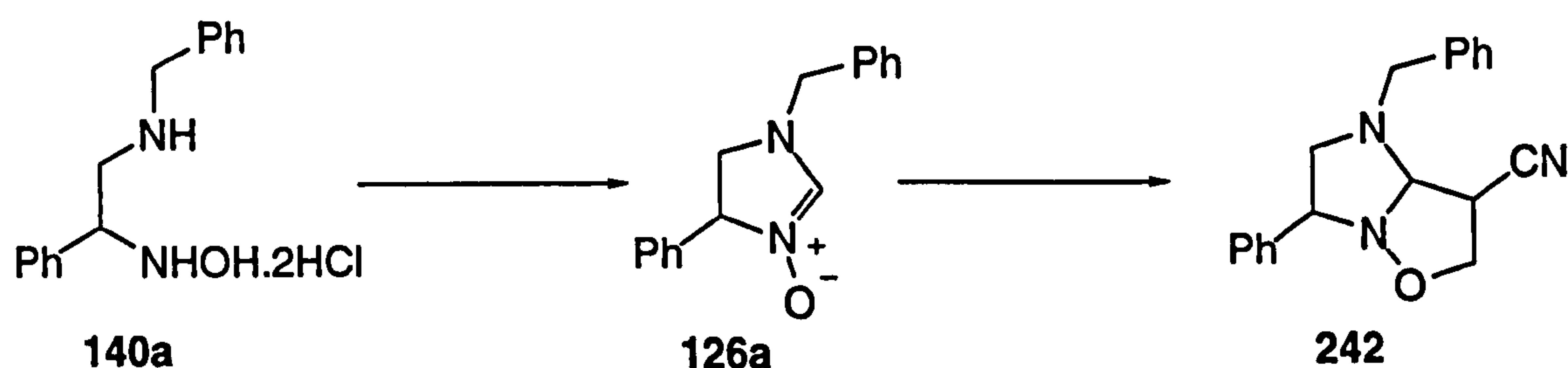
Prepared as for dimethyl maleate cycloadduct **230**, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.300g, 0.952mmol), triethylorthoformate (198 μ l, 1.19mmol), triethylamine (166 μ l, 1.19mmol) and N-methylmaleimide (132mg, 1.19mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOac 4:1 v/v) to afford the *title compound* **239** as an unstable pale yellow oil (202mg, 58%) (Found: MH⁺ 364.1675. C₂₁H₂₁N₃O₃ requires M⁺ 364.1661); ν_{\max} (CHCl₃ soln.) /cm⁻¹ 3026, 1719, 1665, 1500, 1385, 1228, 1191, 909, 701; δ_{H} (CDCl₃; 400MHz) 2.56 (t, 1H, *J* 9.2Hz, PhCHCHHN), 2.98 (s, 3H, NCH₃), 3.60 (m, 3H, PhCHCHHN, NCHHPh & NCHCHC=O), 4.01 (d, 1H, *J* 15.4Hz, NCHHPh), 4.27 (s, 1H, NCHCHC=O), 4.61 (t, 1H, *J* 7.7Hz, PhCHCH₂N), 4.97 (d, 1H, *J* 7.7Hz, NOCHC=O), 7.19-7.38 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 25.0 (NCH₃), 53.9 (NCHCHC=O), 56.4 (NCH₂Ph), 59.9 (PhCHCH₂N), 69.1 (PhCHNO), 75.7 (NOCHC=O), 88.2 (NCHCHC=O), 126.5, 127.3, 127.5, 128.1, 128.3 & 128.6 (Ar-CH), 136.8 & 139.3 (Ar-C), 173.8 & 174.3 (2 x C=O) *m/z* 364 (MH⁺, 2%), 253 (5%), 252 (4%), 237 (5%), 235 (2%), 210 (4%), 208 (4%), 105 (14%), 104 (18%) 91 (100%).

**1-Benzyl-3,8-diphenyloctahydro-8*H*-imidazo[1,2-*b*]pyrrolo[3,4-*d*]-
isoxazole-7,9-dione (240)**



Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.200g, 0.634mmol), triethylorthoformate (132 μ l, 0.793mmol), triethylamine (186 μ l, 1.33mmol) and N-phenylmaleimide (0.137g, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the *title compound* **240** as a pale yellow oil (103mg, 38%) (Found: MH⁺ 426.1818. C₂₆H₂₃N₃O₃ requires MH⁺ 426.1818); ν_{\max} (CHCl₃ soln.) /cm⁻¹ 3026, 1714, 1437, 1384, 1288, 701; δ_{H} (CDCl₃; 300MHz) 2.49 (t, 1H, *J* 9.2Hz, PhCHCHHN), 3.63 (m, 3H, PhCHCHHN, NCHHPh & NCHCHC=O), 3.98 (d, 1H, *J* 13.2Hz, NCHHPh), 4.36 (s, 1H, NCHCHC=O), 4.62 (t, 1H, *J* 8.1Hz, PhCHNO), 5.05 (d, 1H, *J* 8.1Hz, NOCHC=O), 7.21-7.42 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 54.4 (NCHCHC=O), 56.6 (NCH₂Ph), 59.8 (PhCHCH₂N), 68.8 (PhCHNO), 75.6 (NOCHC=O), 88.5 (NCHCHC=O), 126.3, 126.7, 127.5, 127.7, 129.0 & 129.2 (Ar-CH), 131.2, 136.6 & 139.1 (Ar-C), 172.9 & 173.0 (2 x C=O); *m/z* 426 (MH⁺, 36%), 424 (25%), 253 (100%), 252 (63%), 237 (41%), 208 (32%), 174 (12%), 159 (8%), 120 (14%).

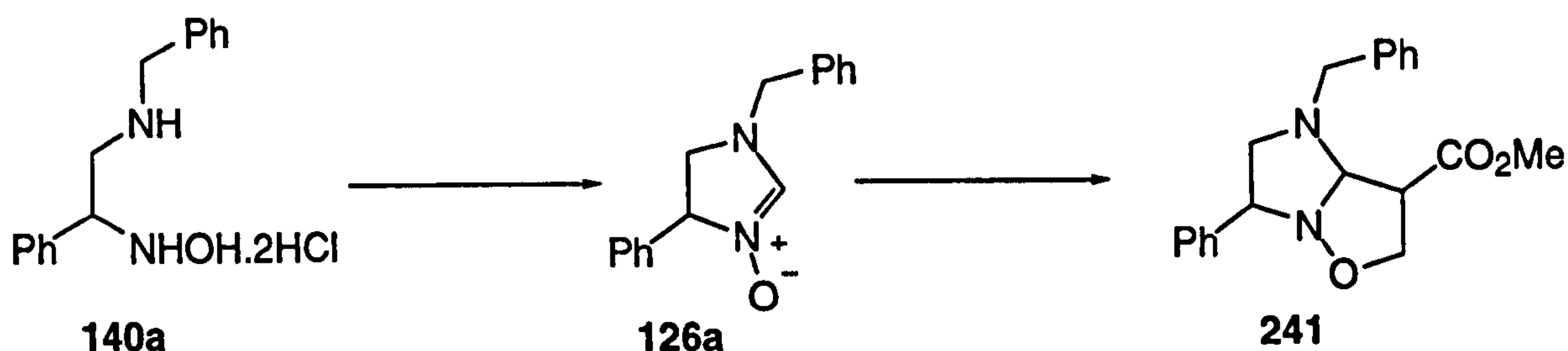
1-Benzyl-6-cyano-3-phenylhexahydroimidazo[1,2-*b*]isoxazole (242)



Prepared as for dimethyl maleate cycloadduct **230**, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.200g, 0.634mmol), triethylorthoformate (132μl, 0.793mmol), triethylamine (186μl, 1.33mmol) and acrylonitrile (52.0μl, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford a mixture of two related compounds which could not be separated. One was assigned on the basis of comparison to analogous structures as the *title compound* **242** (44mg, <23%); δ_{H} (CDCl₃; 400MHz) 2.52 (t, 1H, *J* 10.6Hz, PhCHCHHN), 2.88 (d, 1H, 3.8Hz, NCHCHC≡N), 3.42 (dd, 1H, *J* 7.5, 10.6Hz, PhCHCHHN), 3.77 (2 x d, 2H, *J* 12.2Hz, NCH₂Ph), 4.02 (m, 2H, NOCH₂), 4.33 (m, 1H, PhCHCH₂N), 4.48 (s, 1H, NCHCHC≡N); δ_{C} (CDCl₃; 100MHz) 41.0 (NCHCHC≡N), 58.0 (NCH₂Ph), 59.0 (PhCHCH₂N), 66.3 (NOCH₂), 67.7 (PhCHCH₂N), 88.8 (NCHCHC≡N), 118.6 (C≡N), 126.9, 127.6, 127.7, 128.5, 129.0 & 129.4 (Ar-CH), 136.6 & 138.5 (Ar-C).

1-Benzyl-7-methoxycarbonyl-3-phenylhexahydroimidazo[1,2-*b*]isoxazole

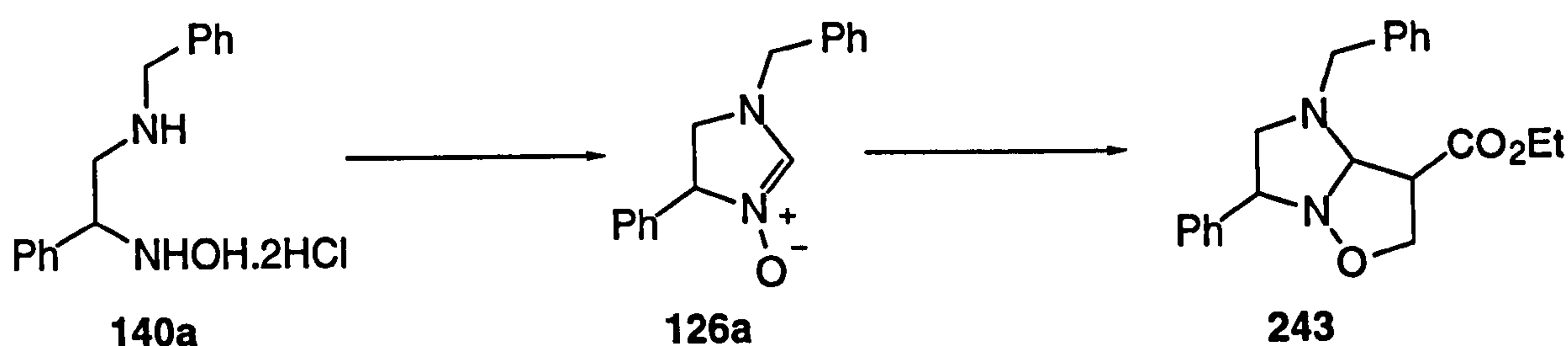
(241)



Prepared as for dimethyl maleate cycloadduct **230**, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (3.62g, 11.5mmol), triethylorthoformate (2.39cm³, 14.4mmol), triethylamine (3.36cm³, 24.2mmol) and methyl acrylate (1.29cm³, 14.4mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the *title compound* **241** as a pale yellow oil (1.30g, 3.84mmol). (Found: C, 67.03; H, 7.02; N, 8.02%; MH⁺ 339.1721. C₂₀H₂₂N₂O₃ + H₂O requires C, 67.40; H, 6.79; N, 7.86%; MH⁺, 339.1709); ν_{\max} (film) /cm⁻¹ 3029, 2951, 2876, 1738, 1662, 1496, 1454, 1437, 1273, 1197, 1175, 747, 702; δ_{H} (CDCl₃; 300MHz) 2.45 (t, 1H, *J* 10.4Hz, PhCHCHHN), 3.10 (d, 1H, *J* 4.0Hz, CHCO₂CH₃), 3.36 (dd, 1H, *J* 6.1, 10.4Hz, PhCHCHHN), 3.61 (d, 1H, *J* 12.8Hz, NCHHPh), 3.71 (s, 3H, CO₂CH₃), 3.92 (d, 1H, *J* 12.8Hz, NCHHPh), 4.21 (m, 2H, NOCH₂), 4.37 (dd, 1H, *J* 6.1, 10.4Hz, PhCHNO), 5.29 (s, 1H, NCHCHCO₂CH₃), 7.23-7.41 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 52.2 (CO₂CH₃), 55.3 (CHCO₂CH₃), 57.7 (NCH₂Ph), 59.0 (PhCHCH₂N), 66.2 (NOCH₂), 68.1 (PhCHNO), 87.6 (NCHCHCO₂CH₃), 126.9, 127.4, 127.5, 128.2 & 129.1 (Ar-CH), 137.3 & 139.3 (Ar-C), 171.2 (C=O); *m/z* 339 (MH⁺, 2%), 307 (0.3%), 253 (2%), 238 (4%), 208 (5%), 104 (22%), 91 (100%).

1-Benzyl-7-ethoxycarbonyl-3-phenylhexahydroimidazo[1,2-*b*]isoxazole

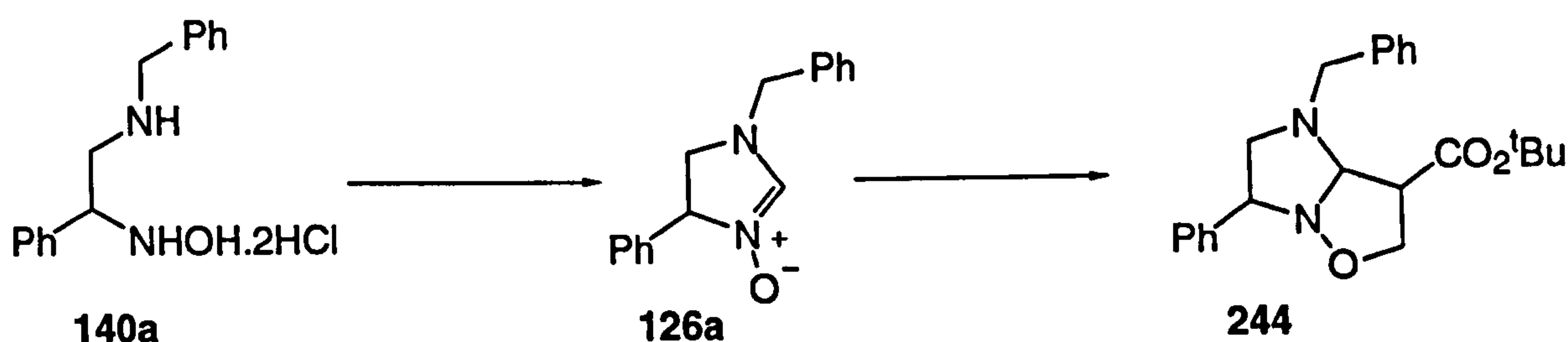
(243)



Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthoformate (132μl, 0.793mmol), triethylamine (186μl, 1.33mmol) and ethyl acrylate (86μl, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the *title compound* 243 as a colourless oil (99.0mg, 44%) (Found: C, 71.26; H, 6.91; N, 8.02%; MH⁺ 353.1842. C₂₁H₂₄N₂O₃ requires C, 71.57; H, 6.86; N, 7.94%; MH⁺ 353.1865); ν_{max} (film) /cm⁻¹ 3063, 3030, 2981, 2875, 2811, 1734, 1496, 1454, 1370, 1305, 1273, 1186, 1126, 1059, 1029, 913, 736, 701; δ_H (CDCl₃; 400MHz) 1.27 (t, 3H, *J* 7.1Hz, CO₂CH₂CH₃), 2.45 (dd, 1H, *J* 9.4, 10.8Hz, PhCHCHHN), 3.08 (m, 1H, CHCO₂CH₂CH₃), 3.36 (dd, 1H, *J* 6.2, 9.4Hz, PhCHCHHN), 3.62 & 3.92 (each d, 1H, *J* 12.8Hz, NCH₂Ph), 4.15 (q, 2H, *J* 7.1Hz, CO₂CH₂CH₃), 4.20 (m, 1H, NOCHH), 4.26 (dd, 1H, *J* 2.4, 9.0Hz, NOCHH), 4.38 (dd, 1H, *J* 6.2, 10.8Hz, PhCHNO), 4.61 (s, 1H, NCHCHCO₂CH₂CH₃), 7.21-7.42 (m, 10H, Ar-H); δ_C (CDCl₃; 100MHz) 14.1 (CO₂CH₂CH₃), 55.4 (CHCO₂CH₂CH₃), 57.7 (NCH₂Ph), 59.0 (PhCHCH₂N), 61.2 (CO₂CH₂CH₃), 66.3 (NOCH₂), 68.1 (PhCHNO), 87.5 (NCHCHCO₂CH₂CH₃), 127.1, 127.4, 127.5, 128.4, 128.5 & 129.1 (Ar-CH), 137.3

& 139.4 (Ar-C), 170.8 (CO₂CH₂CH₃); *m/z* 353 (M⁺, 100%), 275 (12%), 253 (31%), 252 (71%), 248 (33%), 210 (12%), 208 (15%), 174 (15%).

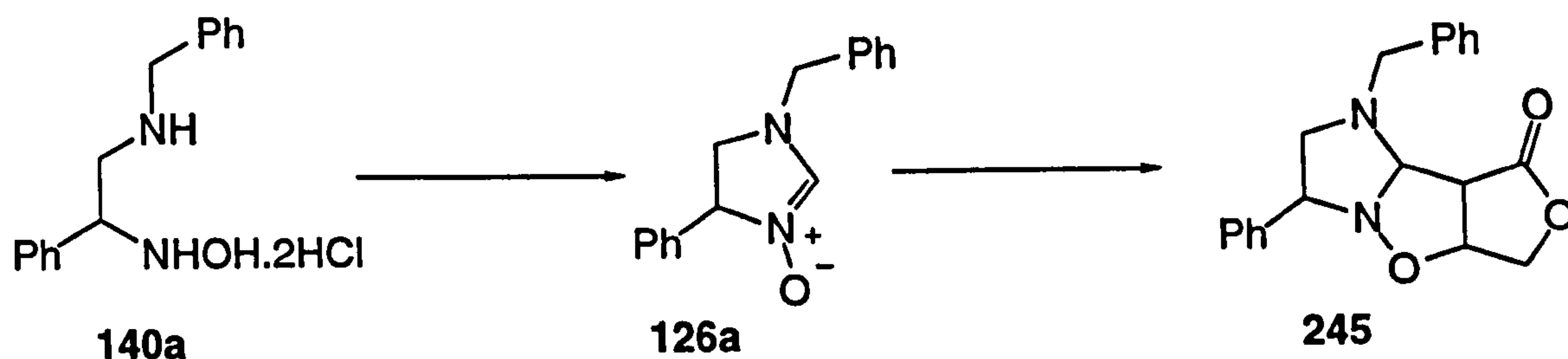
1-Benzyl-7-*tert*-butoxycarbonyl-3-phenylhexahydroimidazo[1,2-*b*]isoxazole
(244)



Prepared as for dimethyl maleate cycloadduct **230**, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.200g, 0.634mmol), triethylorthoformate (132μl, 0.793mmol), triethylamine (186μl, 1.33mmol) and *tert*-butyl acrylate (116μl, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the *title compound* **244** as a colourless oil (20.0mg, 8%). (Found: MH⁺ CI 381.2178. C₂₃H₂₈N₂O₃ requires MH⁺ 381.2178); ν_{\max} (CHCl₃) /cm⁻¹ 2982, 2932, 1725, 1606, 1455, 1394, 1370, 1156, 1030, 846, 810; δ_{H} (CDCl₃; 400MHz) 1.47 (s, 9H, CO₂C(CH₃)₃), 2.46 (dd, 1H, *J* 9.5, 10.8Hz, PhCHCHHN), 3.02 (m, 1H, CHCO₂C(CH₃)₃), 3.35 (dd, 1H, *J* 6.2, 9.5Hz, PhCHCHHN), 3.60 & 3.93 (each d, 2H, *J* 12.8Hz, NCH₂Ph), 4.19 (m, 2H, NOCH₂), 4.37 (m, 1H, PhCHNO), 4.55 (s, 1H, NCHCHCO₂C(CH₃)₃), 7.22-7.39 (m, 10H, Ar-H); δ_{C} (CDCl₃; 100MHz) 28.0 (C(CH₃)₃), 56.3 (CHCO₂C(CH₃)₃), 57.7 (NCH₂Ph), 59.0 (PhCHCH₂N), 66.5 (NOCH₂), 68.0 (PhCHNO), 81.6 (C(CH₃)₃), 87.7 (NCHCHCO₂C(CH₃)₃), 127.1, 127.4, 127.5, 128.4,

128.5 & 129.1 (Ar-CH), 137.4 & 139.4 (Ar-C), 170.8 (C=O); m/z 381 (MH^+ , 3%), 325 (2%), 323 (2%), 307 (1%), 252 (6%), 237 (3%), 210 (6%), 91 (100%).

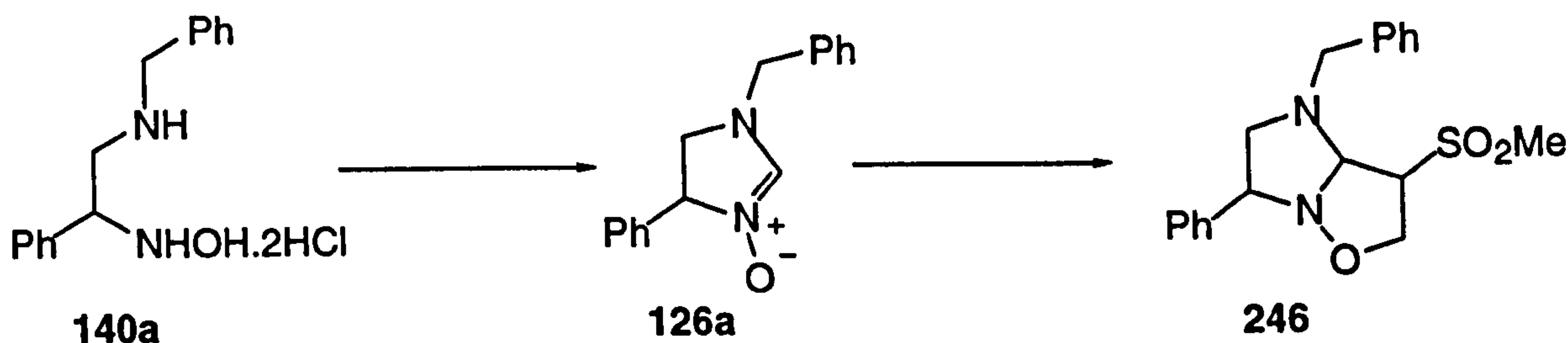
1-Benzyl-3-phenyloctahydro-1*H*-imidazo[1,2-*b*]furo[3,4-*d*]isoxazol-9-one
(245)



Prepared as for dimethyl maleate **230**, cycloadduct using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride **140a** (0.200g, 0.634mmol), triethylorthoformate (132 μ l, 0.793mmol), triethylamine (186 μ l, 1.33mmol) and 2(5*H*)-furanone (56.0 μ l, 0.793mmol). The crude material was purified by column chromatography (SiO_2 , hexane:EtOAc 4:1 v/v) to afford the *title compound* **245** as an unstable colourless oil (89.0mg, 42%). (Found: MH^+ 337.1567; $C_{20}H_{20}N_2O_3$ requires MH^+ 337.1552); δ_H ($CDCl_3$; 400MHz) 2.42 (t, 1H, J 9.5, 10.7Hz, $PhCHCHHN$), 3.13 (d, 1H, J 5.3Hz, $NCHCHC=O$), 3.26 (dd, 1H, J 6.0, 9.5Hz, $PhCHCHHN$), 3.64 and 3.84 (each d, 1H, J 12.8Hz, NCH_2Ph), 4.29 (d, 2H, J 1.8Hz, $NOCHCH_2O$), 4.36 (dd, 1H, J 6.0, 10.7Hz, $PhCHNO$), 4.54 (s, 1H, $NCHCHC=O$), 4.98 (dt, 1H, J 1.8, 5.3Hz, $NOCHCH_2O$); δ_C ($CDCl_3$; 100MHz) 56.2 ($NCHCHC=O$), 57.7 (NCH_2Ph), 58.6 ($PhCHCH_2N$), 68.2 ($PhCHNO$), 69.9 ($NOCHCH_2O$), 76.2 ($NOCHCH_2O$), 88.6 ($NCHCHC=O$), 126.8,

127.4, 127.5, 128.2, 128.3 & 129.1 (Ar-CH), 136.7 & 138.4 (Ar-C), 174.5 (C=O); m/z 337 (MH^+ , 21%), 253 (11%), 238 (8%), 210 (6%), 139 (15%), 91 (100%).

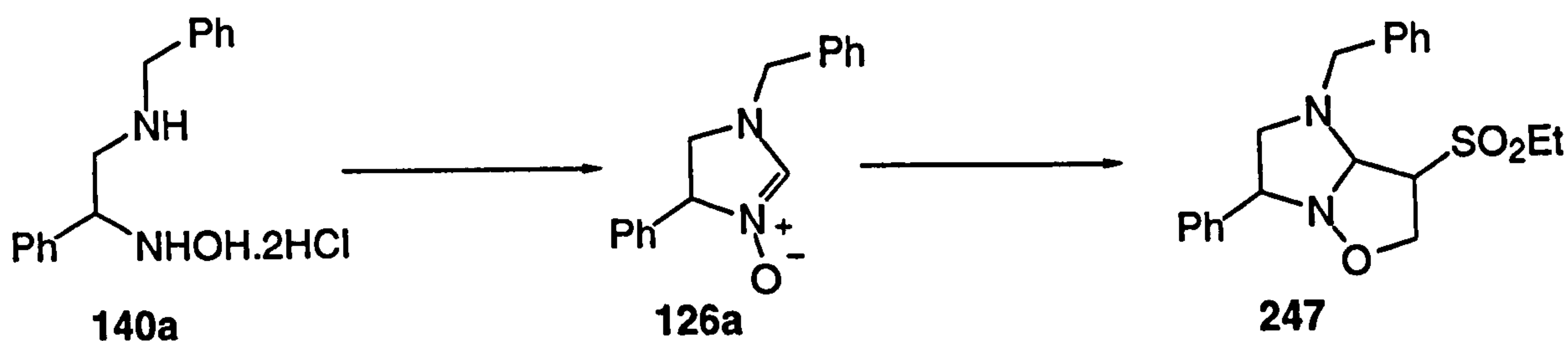
1-Benzyl-7-methylsulfonyl-3-phenylhexahydroimidazo[1,2-*b*]isoxazole (246)



Prepared as for dimethyl maleate 230, cycloadduct using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthoformate (132 μ l, 0.793mmol), triethylamine (186 μ l, 1.33mmol) and methyl vinyl sulfone (89.0 μ l, 0.793mmol). The crude material was purified by column chromatography (SiO_2 , hexane:EtOAc 4:1 v/v) to afford the *title compound* 246 as a colourless oil (95.0mg, 42%) (Found: C, 61.69%; H, 6.09%; N, 7.46%; MH^+ 359.1420. $C_{19}H_{22}N_2O_3S + 0.6H_2O$ requires C, 61.80%; H, 6.33%; N, 7.59%; MH^+ 359.1429); ν_{max} (film) / cm^{-1} 3062, 3029, 2929, 2876, 2820, 1655, 1455, 1305, 1130, 971, 751, 702; δ_H ($CDCl_3$; 400MHz) 2.46 (t, 1H, J 9.8Hz, $PhCHCHHN$), 2.90 (s, 3H, SO_2CH_3), 3.31 (dd, 1H, J 6.1, 9.8Hz, $PhCHCHHN$), 3.59 (d, 1H, J 13.2Hz, $NCHHPh$), 3.65 (br s, 1H, $CHSO_2CH_3$), 4.04 (d, 1H, J 13.2Hz, $NCHHPh$), 4.37 (dd, 1H, J 6.1, 9.8Hz, $PhCHNO$), 4.40 (d, 2H, J 3.1Hz, $NOCH_2$), 4.62 (s, 1H, $NCHCHSO_2CH_3$), 7.24-7.41 (m, 10H, Ar-H); δ_C ($CDCl_3$; 100MHz) 39.3 (SO_2CH_3), 56.9 (NCH_2Ph), 57.8 ($PhCHNO$), 64.3 ($NOCH_2$), 68.1 ($PhCHCH_2N$), 74.5 ($CHSO_2CH_3$), 85.6 ($NCHCHSO_2CH_3$), 126.9,

127.7, 128.5, 128.6 & 129.1 (Ar-CH), 136.2 & 138.4 (Ar-C); m/z 359 (MH^+ , 3%), 279 (2%), 252 (2%), 237 (3%), 210 (5%), 208 (4%), 105 (27%), 104 (47%), 91 (100%), 61 (73%), 45 (90%).

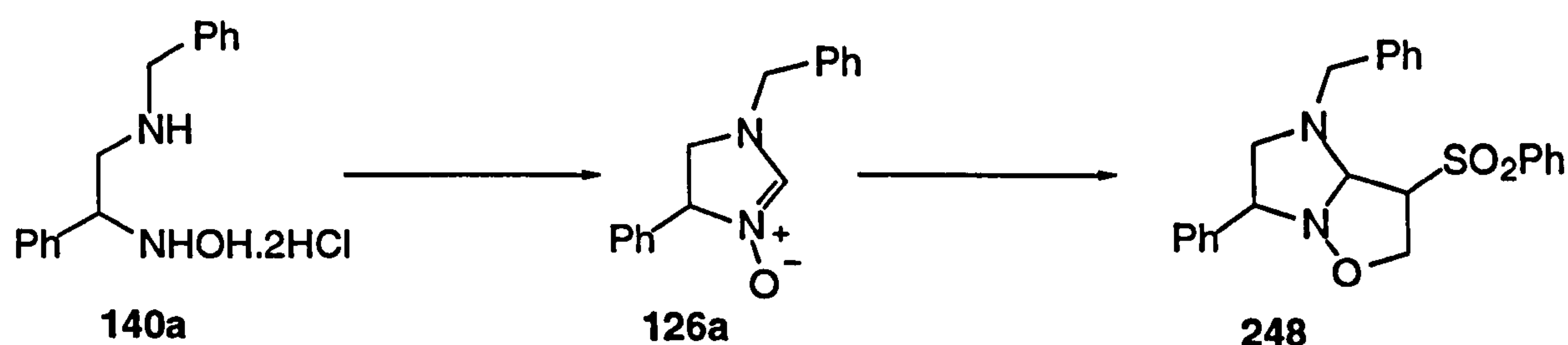
1-Benzyl-7-ethylsulfonyl-3-phenylhexahydroimidazo[1,2-*b*]isoxazole (247)



Prepared as for dimethyl maleate cycloadduct using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride (0.200g, 0.634mmol), triethylorthoformate (132 μ l, 0.793mmol), triethylamine (186 μ l, 1.33mmol) and ethyl vinyl sulfone (83.0 μ l, 0.793mmol). The crude material was purified by column chromatography (SiO_2 , hexane:EtOAc 4:1 v/v) to afford the *title compound* **247** as a pale yellow oil (69.0mg, 29%) (Found: C, 64.34%; H, 6.58%; N, 7.37%; MH^+ 373.1587. $C_{20}H_{22}N_2O_3S$ requires C, 64.49%; H, 6.49%; N, 7.52%); MH^+ 373.1586; ν_{max} (film) / cm^{-1} 3063, 3030, 2943, 2879, 2818, 1496, 1455, 1357, 1308, 1235, 1120, 1029, 915, 794, 736, 701; δ_H ($CDCl_3$, 300MHz) 1.40 (t, 3H, J 7.3Hz, $SO_2CH_2CH_3$), 2.44 (dd, 1H, J 9.4, 10.8Hz, PhCHCHHN), 3.00 (q, 2H, J 7.3Hz, $SO_2CH_2CH_3$), 3.31 (dd, 1H, J 6.1, 9.4Hz, PhCHCHHN), 3.59 (d, 1H, J 13.2Hz, NCHHPh), 3.70 (t, 1H, J 3.3Hz, NCHCH $SO_2CH_2CH_3$), 4.04 (d, 1H, J 13.2Hz, NCHHPh), 4.34 (m, 1H, PhCHNO), 4.38 (d, 2H, J 3.7Hz, NOCH $_2$), 4.63 (s, 1H, NCHCH $SO_2CH_2CH_3$), 7.22-7.38 (Ar-H); δ_C

(CDCl₃; 100MHz) 5.4 (SO₂CH₂CH₃), 46.2 (SO₂CH₂CH₃), 57.2 (NCH₂Ph), 57.9 (PhCHCH₂N), 64.6 (NOCH₂), 68.2 (PhCHNO), 73.7 (CHSO₂CH₂CH₃), 85.6 (NHCHCHSO₂CH₂CH₃), 127.2, 128.1, 128.9, 129.1 & 129.6 (Ar-CH), 138.4 (Ar-C); *m/z* 373 (MH⁺, 1%), 238 (4%), 237 (2%), 210 (4%), 208 (2%), 132 (2%), 130 (3%), 122 (4%), 105 (13%), 104 (23%), 91 (50%), 61 (62%), 45 (100%).

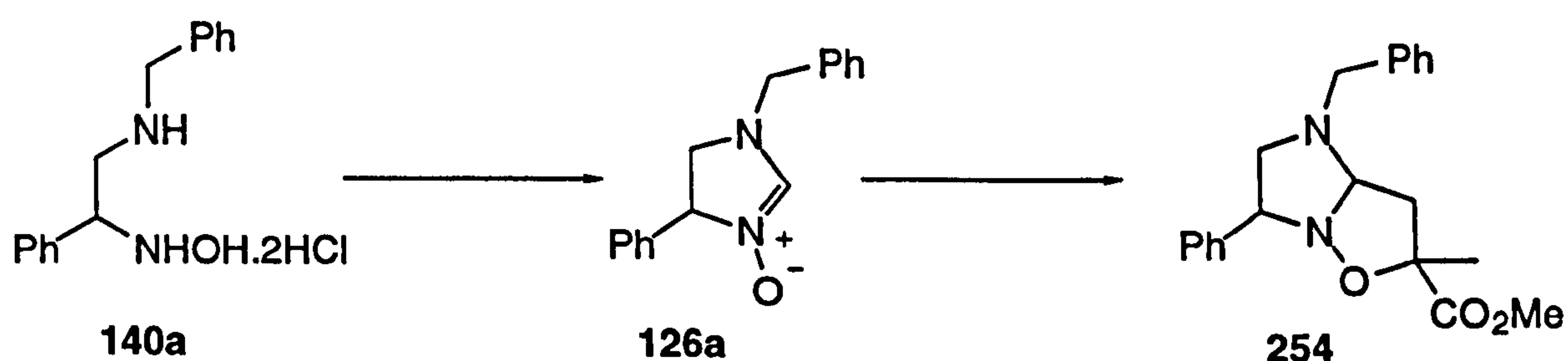
1-Benzyl-3-phenyl-7-phenylsulfonylhexahydroimidazo[1,2-*b*]isoxazole (248)



Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthoformate (132μl, 0.793mmol), triethylamine (186μl, 1.33mmol) and phenyl vinyl sulfone (133mg, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the *title compound* 248 as an off-white white crystalline solid (121mg, 45%). Recrystallisation from methanol afforded white needles crystalline for X-ray crystallographic analysis, mp 105-106°C (Found: C, 68.49%; H, 5.75%; N, 6.66%; MH⁺ 421.1586. C₂₄H₂₄N₂O₃S requires C, 68.55%; H, 5.73%; 6.65%; MH⁺ 421.1586); *v*_{max} (KBr) /cm⁻¹ 3062, 3024, 2969, 2884, 2824, 1496, 1448, 1314, 1196, 1166, 1154, 1089, 745, 725, 701, 590, 548; *δ*_H (CDCl₃, 300MHz) 2.40 (dd, 1H, *J* 9.5, 10.6Hz, PhCHCHHN), 3.27 (dd, 1H, *J* 6.2, 9.5Hz, PhCHCHHN), 3.43 &

3.80 (each d, 1H J 13.2Hz, NCH_2Ph), 3.93 (m, 1H, CHSO_2Ph), 4.33 (m, 3H, PhCHNO & NOCH_2), 4.70 (s, 1H, $\text{NCHCHSO}_2\text{Ph}$), 7.19-7.35 (m, 10H), 7.59 (m, 2H), 7.66 (m, 1H) & 7.96 (m, 2H, Ar-H); δ_{C} (CDCl_3 ; 100MHz) 56.7 (NCH_2Ph), 58.3 (PhCHCH_2N), 64.9 (NOCH_2), 67.3 (PhCHNO), 75.3 (CHSO_2Ph), 85.6 ($\text{NCHCHSO}_2\text{Ph}$), 126.9, 127.6, 127.9, 128.4, 128.5, 128.9 & 129.5 (Ar-CH), 134.3, 137.6 & 138.5 (Ar-C); m/z 421 (MH^+ , 0.3%), 238 (3%), 210 (3%), 105 (16%), 104 (23%), 91 (57%), 61 (57%), 45 (100%).

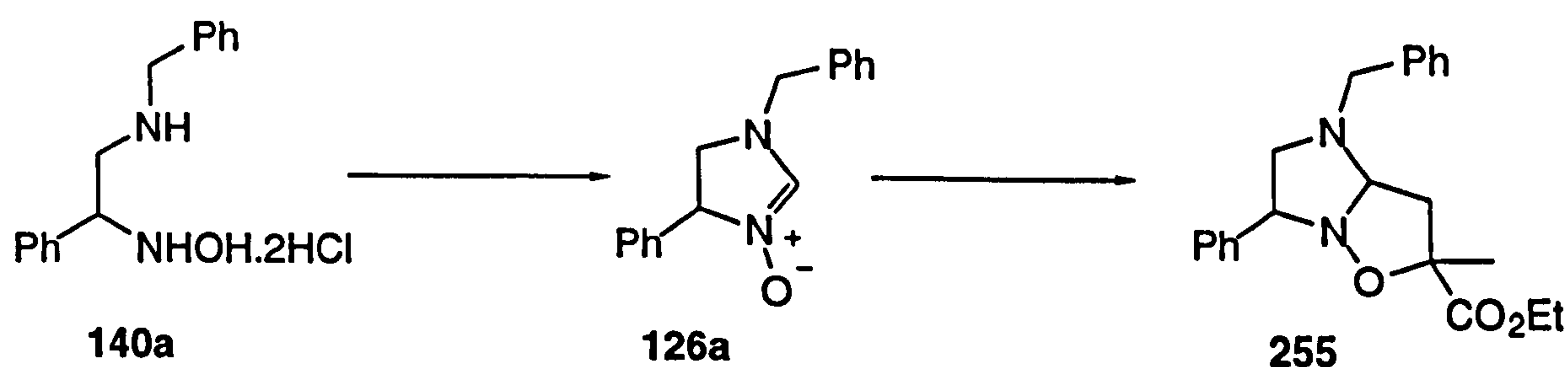
1-Benzyl-6-methoxycarbonyl-6-methyl-3-phenylhexahydro-1*H*-imidazo[1,2-*b*]isoxazole (254)



Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthoformate (132 μ l, 0.793mmol), triethylamine (186 μ l, 1.33mmol) and methyl methacrylate (85.0 μ l, 0.793mmol). The crude material was purified by column chromatography (SiO_2 , hexane:EtOAc 4:1 v/v) to afford the *title compound* 254 as a colourless oil (36.0mg, 16%) (Found: MH^+ 353.1865. $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$ requires M^+ 335.1865); δ_{H} (CDCl_3 ; 400MHz) 1.54 (s, 3H, NOCCH_3), 2.13 (dd, 1H, J 9.6, 10.2Hz, PhCHCHHN), 2.31 (dd, 1H, J 4.9, 12.8Hz, $\text{NCHCHHCCO}_2\text{CH}_3$), 3.09 (d, 1H, J

12.8Hz, NCHCHHCO₂CH₃), 3.15 (d, 1H, *J* 12.5Hz, NCHHPh), 3.32 (dd, 1H, *J* 7.4, 9.6Hz, PhCHCHHN), 3.78 (s, 3H, CO₂CH₃), 3.91 (d, 1H, *J* 12.5Hz, NCHHPh), 4.09 (d, 1H, *J* 4.9Hz, NCHCH₂CO₂CH₃), 4.96 (dd, 1H, *J* 7.4, 10.2Hz, PhCHNO), 7.18-7.40 (m, 10H, Ar-CH); δ_c (CDCl₃; 100MHz) 23.3 (NOCCH₃), 44.1 (NCHCH₂CO₂CH₃), 52.3 (CO₂CH₃), 56.7 (NCH₂Ph), 60.1 (PhCHCH₂N), 71.6 (PhCHNO), 82.2 (NOCCO₂CH₃), 86.3 (NCHCH₂), 126.8, 127.1, 127.3, 128.3, 128.5 & 128.9 (Ar-CH), 137.7 & 140.9 (Ar-C), 175.4 (CO₂CH₃); *m/z* 353 (MH⁺, 16%), 293 (6%), 252 (7%), 237 (6%), 210 (11%), 208 (12%), 174 (25%), 132 (20%), 91 (100%), 77 (13%), 61 (32%).

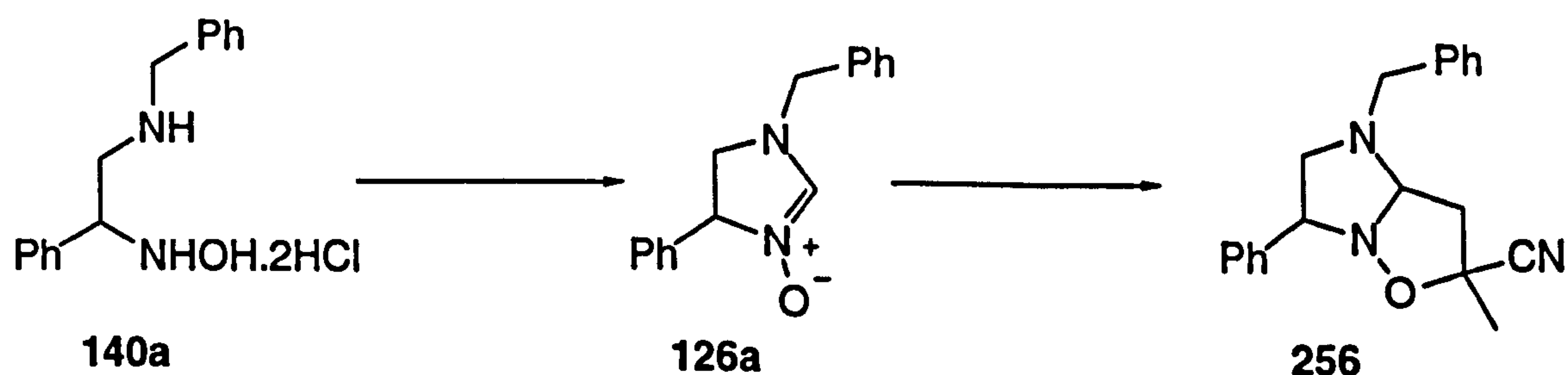
1-Benzyl-6-ethoxycarbonyl-6-methyl-3-phenylhexahydroimidazo[1,2-*b*]isoxazole (255)



Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (2.00g, 6.34mmol), triethylorthoformate (1.32cm³, 7.93mmol), triethylamine (1.86cm³, 13.3mmol) and ethyl methacrylate (0.99cm³, 7.93mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the *title compound* 255 as a colourless oil (312mg, 13%). (Found: MH⁺ 367.2022. C₂₁H₂₄N₂O₃ requires MH⁺ 367.2022); δ_H (CDCl₃; 400MHz) 1.27 (t, 3H, *J* 6.9Hz, CO₂CH₂CH₃), 1.53 (s, 3H,

NOCCH₃), 2.13 (dd, 1H, *J* 9.7, 10.2Hz, PhCHCHHN), 2.29 (dd, 1H, 4.9, 12.9Hz, NCHCHHCO₂CH₂CH₃), 3.14 (m, 2H, NCHHPh & NCHCHHCO₂CH₂CH₃), 3.28 (dd, 1H, *J* 7.4, 9.7Hz, PhCHCHHN), 3.91 (d, 1H, *J* 12.6Hz, NCHHPh), 4.09 (d, 1H, *J* 4.9Hz, NCHCH₂), 4.18 & 4.35 (each m, 1H, CO₂CH₂CH₃), 5.01 (dd, 1H, *J* 7.4, 10.2Hz, PhCHNO), 7.18-7.24 (m, 10H, Ar-H); δ_c (CDCl₃; 100MHz) 14.1 (CO₂CH₂CH₃), 23.3 (NOCCH₃), 44.1 (NCHCH₂), 56.7 (NCH₂Ph), 59.9 (PhCHCH₂N), 61.0 (CO₂CH₂CH₃), 71.5 (PhCHNO), 82.4 (NOCCO₂CH₂CH₃), 86.2 (NCHCH₂CO₂CH₂CH₃), 126.7, 126.8, 127.1, 128.1 & 128.8 (Ar-CH), 137.5 & 140.7 (Ar-C), 174.6 (CO₂CH₂CH₃); *m/z* 367 (MH⁺, 5%), 365 (4%), 293 (3%), 252 (5%), 237 (3%), 210 (6%), 208 (8%), 174 (16%), 132 (13%), 91 (100%), 83 (37%).

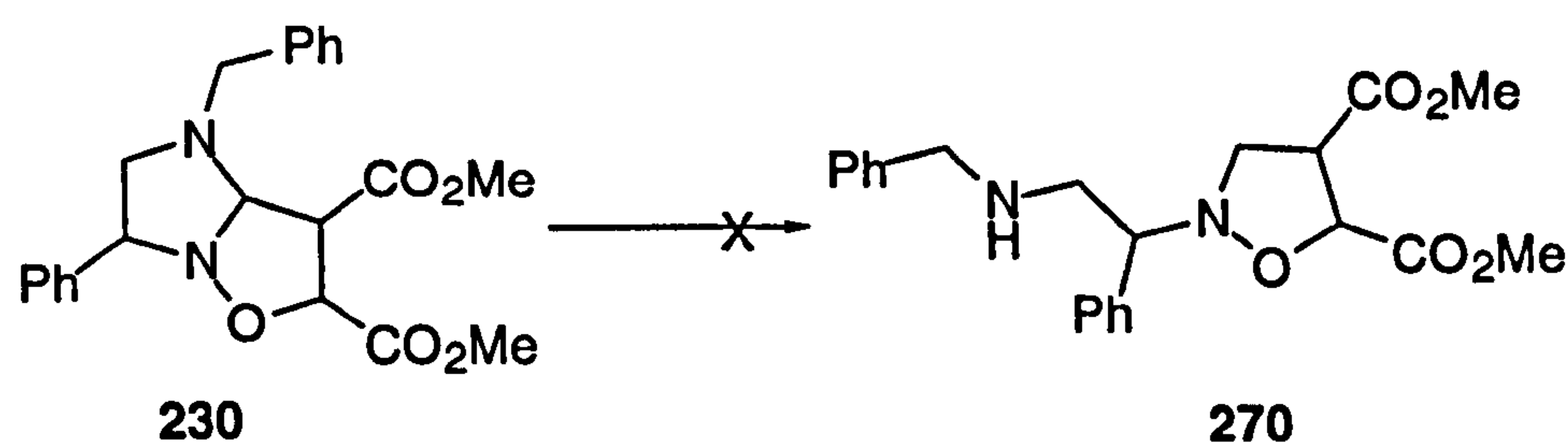
**1-Benzyl-6-cyano-6-methyl-3-phenylhexahydroimidazo[1,2-*b*]isoxazole
(256)**



Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.270g, 0.856mmol), triethylorthoformate (178μl, 1.07mmol), triethylamine (149μl, 1.07mmol) and methacrylonitrile (90.0μl, 1.07mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford a mixture from which the *title*

compound **256** was tentatively assigned by comparison with similar structures as a colourless oil (14.0mg, <5%); δ_{H} (CDCl_3 ; 400MHz) 1.70 (s, 3H, NOCCH_3), 2.28 (m, 2H, PhCHCHHN & $\text{NCHCHHCC}\equiv\text{N}$), 2.62 (d, 1H, J 13.2Hz, $\text{NCHCHHCC}\equiv\text{N}$), 3.52 (m, 2H, NCHHPh & PhCHCHHN), 3.90 (d, 1H, J 13.2Hz, NCHHPh), 4.33 (d, 1H, J 5.6Hz, $\text{NCHCH}_2\text{CC}\equiv\text{N}$), 4.99 (m, 1H, PhCHNO).

Attempted preparation of 2-benzylamino-1phenylethyl-4,5-dimethoxycarbonyltetrahydroisoxazole (**270**)

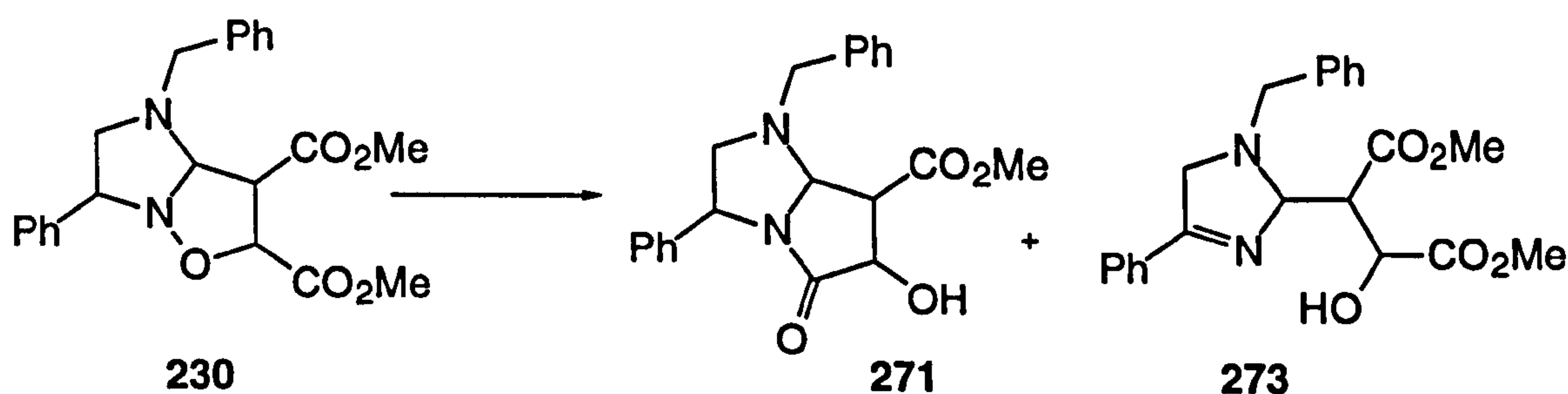


A solution of cycloadduct **230** (0.130g, 0.328mmol) in absolute ethanol (5cm^3) was treated with sodium cyanoborohydride (25.0mg, 0.361mmol) in one portion and the solution kept acidic to bromocresol green indicator with aqueous HCl (2M), but no change was observed by TLC analysis after 48 h at 20°C . In a similar experiment, an ethanol solution of **230** with sodium cyanoborohydride was heated to reflux for 1.5 h. Upon cooling to 20°C , the solvent was removed under reduced pressure, but only unchanged **230** was identified from the residue.

A glacial acetic acid solution (5cm^3) of **230** (0.100g, 0.252mmol) was treated with sodium cyanoborohydride (17.0mg, 0.271mmol) in one portion and stirred at 20°C for 18 h. The solution was basified with aqueous NaOH (2M) before extraction into DCM (3 x

30cm³) which was then dried (MgSO₄) and filtered. The solvent was removed under reduced pressure but no desired material was isolated from the residue after column chromatography (SiO₂, EtOAc). A similar protocol in which the solution was heated to 100°C for 2 h returned an intractable black tar with these reagents.

1-Benzyl-6-hydroxy-7-methoxycarbonyl-3-phenylhexahydro-5H-pyrrolo[1,2,-a]imidazol-5-one (271)



A solution of dimethyl maleate cycloadduct **230** (0.764g, 1.93mmol) in methanol (30cm³) was treated with W-2 Raney Nickel (from a 50% slurry in water) (approx. 6g of Ni), and agitated under an atmosphere of hydrogen at 65psi (Parr hydrogenator) for 18 h. The mixture was filtered and the filtrate evaporated to dryness. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the *title compound* **271** as an off-white solid (415mg, 59%) along with an impure compound assigned, after further purification by careful chromatography as described above, as 1-benzyl-2-[1-(2-hydroxy-1,2-bis-methoxycarbonyl)ethyl]-4-phenyl-2,4-dihydro-1H-imidazole **273** (16.0mg, 2%); δ_{H} (CDCl₃; 400MHz) 3.18 (dd, 1H, *J* 3.1, 6.7Hz, NCHCHCO₂CH₃), 3.64 (d, 1H, *J* 13.4Hz, NCHHPh), 3.74 & 3.77 (each s, 3H, 2 x CO₂CH₃), 3.80 (m, 1H, PhCCHHN), 4.22 (m, 2H, PhCCHHN & NCHHPh), 4.81 (d, 1H, *J* 3.1Hz, NCHCHCO₂CH₃), 5.55 (m, 1H,

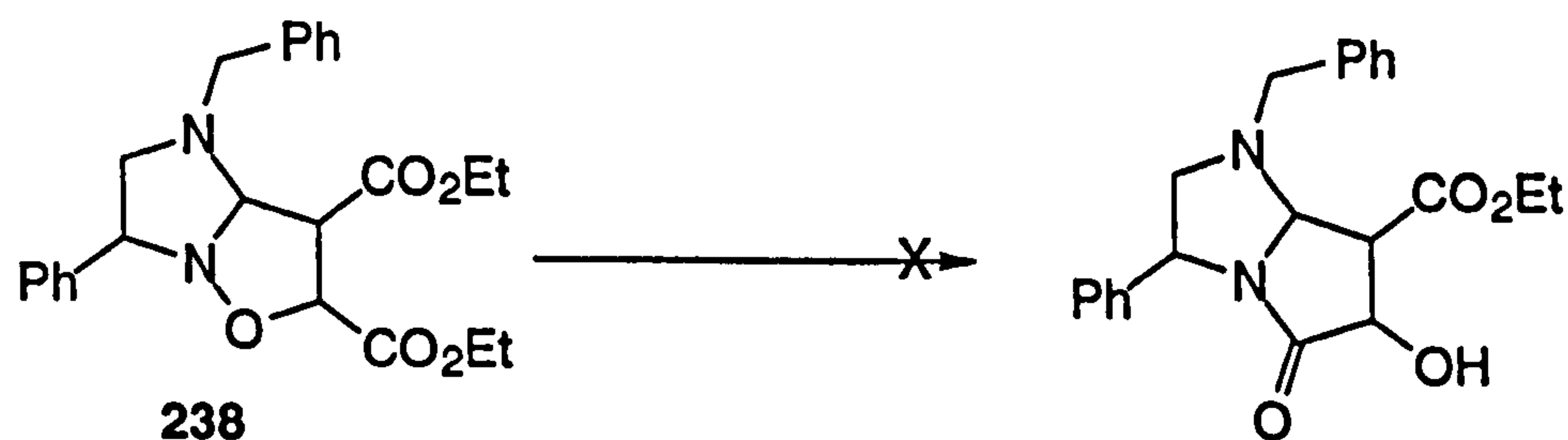
CHOH); δ_c (CDCl₃; 100MHz) 52.1 & 52.4 (2 x CO₂CH₃), 54.3 (NCHCHCO₂CH₃), 59.6 (NCH₂Ph), 61.0 (PhCCH₂N), 69.9 (NCHCHCO₂CH₃), 92.6 (CHOH), 127.3, 127.8, 128.3, 128.5, 128.6 & 138.9 (Ar-CH), 131.5 & 131.8 (Ar-C), 170.8, 171.0 & 173.2 (2 x CO₂CH₃ & PhC=N).

The relative stereochemistry of lactam **271** was determined by NOESY in CDCl₃ and d₆-DMSO. A sample was later recrystallised from methanol to afford small, white needles which, by X-ray crystallographic analysis, confirmed our assignments, mp 131-132°C (Found: C, 68.80; H, 6.07; N, 7.58%; MH⁺ 367.1652. C₂₁H₂₂N₂O₄ requires C, 68.84; H, 6.05; N, 7.64%; MH⁺ 367.1658); ν_{\max} (KBr) /cm⁻¹ 3344, 2898, 2827, 1742, 1686, 1438, 1330, 1315, 1287, 1268, 1132, 1120 1017, 750, 703, 697; δ_H (CDCl₃; 300MHz) 2.53 (t, 1H, *J* 9.5Hz, PhCHCHHN), 3.17 (dd, 1H, *J* 5.3, 9.3Hz, CHCO₂CH₃), 3.42 (d, 1H, *J* 12.9Hz, NCHHPh), 3.55 (br s, OH), 3.67 (dd, 1H, *J* 7.8, 9.5Hz, PhCHCHHN), 3.74 (s, 3H, CO₂CH₃), 3.99 (d, 1H, *J* 12.9Hz, NCHHPh), 4.52 (d, 1H, *J* 5.3Hz, NCHCHCO₂CH₃), 4.90 (d, 1H, *J* 9.3Hz, CHOH), 5.02 (dd, 1H, *J* 7.8, 9.5Hz, PhCHNC=O) 7.17-7.37 (m, 10H, Ar-H); δ_c (CDCl₃; 100MHz) 52.7 (CO₂CH₃), 55.7 (NCH₂Ph), 55.9 (CHCO₂CH₃), 57.2 (PhCHNC=O), 62.2 (PhCHCH₂N), 74.8 (CHOH), 79.3 (NCHCHCO₂CH₃), 125.8, 127.6, 127.7, 128.5, 128.7 & 128.8 (Ar-CH), 136.9 & 139.4 (Ar-C), 171.6 & 174.0 NC=O & CO₂CH₃); δ_H (d₆-DMSO; 300MHz) 2.41 (t, 1H, *J* 9.4Hz, PhCHCHHN), 2.94 (dd, 1H, *J* 5.4, 9.5Hz, CHCO₂CH₃), 3.44 (d, 1H, *J* 13.0Hz, NCHHPh), 3.58 (dd, 1H, *J* 7.6, 9.4Hz, PhCHCHHN), 3.66 (s, 3H, CO₂CH₃), 3.87 (d, 1H, *J* 13.0Hz, NCHHPh), 4.41 (d, 1H, *J* 5.4Hz, NCHCHCO₂CH₃), 4.71 (dd, 1H, *J* 7.4, 9.5Hz, CHOH), 4.85 (dd, 1H, *J* 7.6, 9.4Hz, PhCHNC=O), 6.13 (d, 1H, *J* 7.4Hz, OH), 7.23-7.34 (m, 10H, Ar-H); *m/z* 367 (MH⁺, 30%), 123 (27%), 105 (100%), 91 (80%), 61 (32%), 45 (38%).

In a similar experiment, a slurry of the cycloadduct **230** (100mg, 0.252mmol) and 5% Pd-C (27mg, 5mol%) in methanol (5cm³) was stirred at 30°C under hydrogen (1 atmos.) at 20°C for 18 h. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the title compound **271** as a colourless gum (13.0mg, 14%).

The cycloadduct **230** (0.100g, 0.252mmol) was also dissolved in methanol (5cm³), treated with 10% Pd(OH)₂-C (27.0mg, 5mol%) and stirred under hydrogen (1 atmos.) for 18 h. The solution was filtered, the filtrate evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the lactam **271** (25.0mg, 27%).

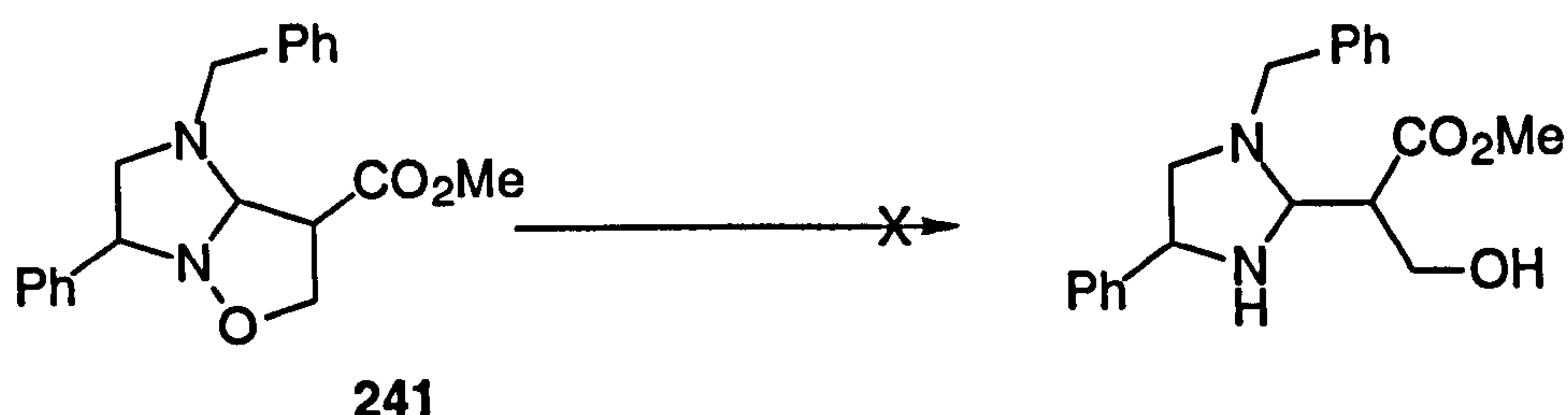
Attempted preparation of 1-benzyl-7-ethoxycarbonyl-6-hydroxy-3-phenylhexahydro-5H-pyrrolo[1,2,-a]imidazol-5-one



A solution of the diethyl maleate cycloadduct **238** (100mg, 0.236mmol) in methanol (5cm³) was treated with W-2 Raney Nickel (from a 50% slurry in water w/w) (approx. 200mg of Ni), and agitated under an atmosphere of hydrogen (65psi; Parr hydrogenator) for 18 h. The mixture was filtered and the filtrate evaporated to dryness but none of the title

compound was isolated from the mixture of products after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v).

Attempted preparation of 1-benzyl-2-(1-methoxycarbonyl-2-hydroxyethyl)-4-phenyltetrahydroimidazole

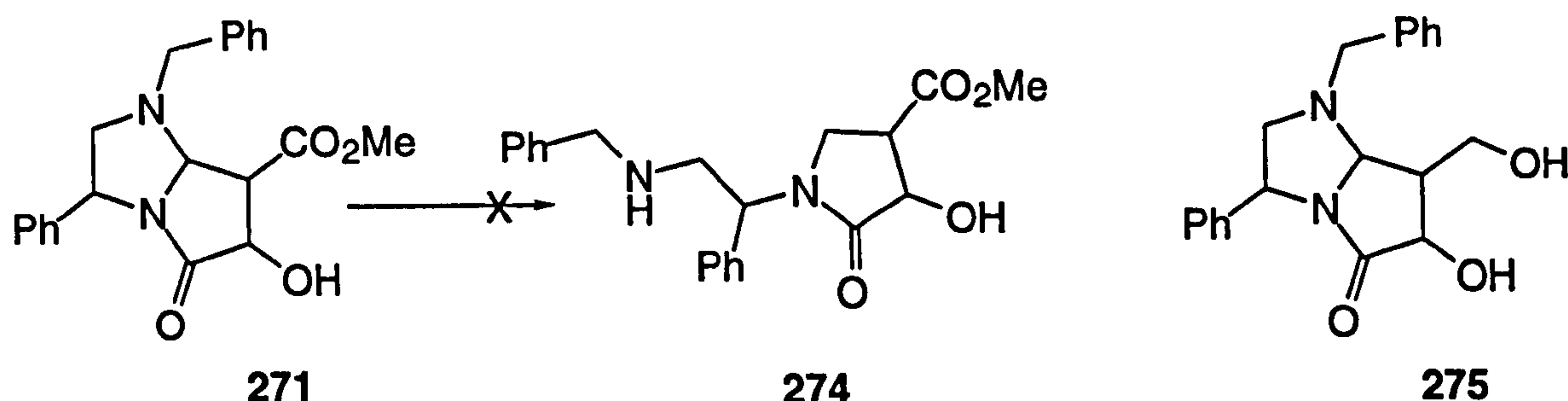


A solution of methyl acrylate cycloadduct **241** (100mg, 0.295mmol) in MeOH (10cm³) was treated with 10% Pd-C (31mg, 5mol%) and kept under hydrogen (1 atmos.) at 20°C and atmospheric pressure for 48 h. The mixture was filtered and the solvent evaporated under reduced pressure to return the starting material unchanged.

Hydrogenolysis was also attempted using the cycloadduct **241** (100mg, 0.295mmol) in methanol (10cm³) with 20% Pd(OH)₂-C (16mg, 5mol%) under hydrogen (1 atmos.) at 20°C for 18 h. Column chromatography (SiO₂, CHCl₃:ⁱPrNH₂ 200:1 v/v) failed to return any identifiable material from the crude product mixture.

A similar experiment used the cycloadduct **241** (100mg, 0.295mmol) and W-2 Raney Nickel (from a 50% slurry in water w/w) (approx. 1g of Ni) in methanol (10cm³). After 18 h at 60psi, the mixture was filtered and the filtrate evaporated. The residue returned no identified products after column chromatography (SiO₂, CHCl₃:ⁱPrNH₂ 200:1 v/v).

Attempted preparation of 1-(2-benzylamino-1-phenylethyl)-3-hydroxy-4-methoxycarbonyltetrahydropyrrol-2-one (274)

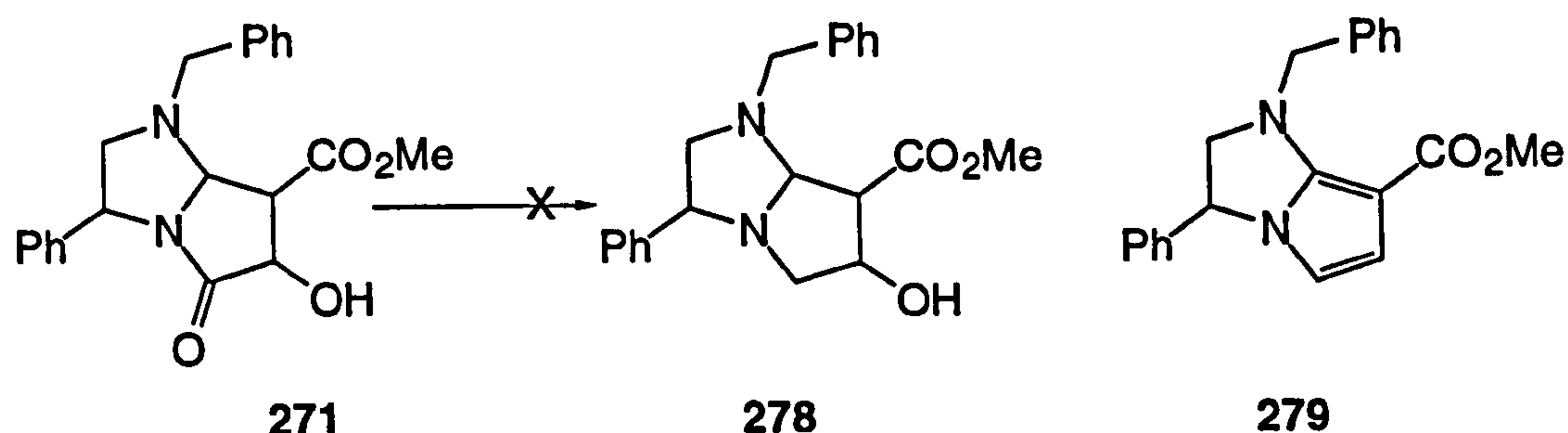


Using the procedures described for the attempted cleavage of **230** above, **271** was reacted with sodium cyanoborohydride in ethanol at pH3 at 20°C and in glacial acetic acid at reflux. Neither experiment returned any of the title compound.

A solution of lactam **271** (80.0mg, 0.218mmol) in dry distilled THF (5cm³) under nitrogen was treated with sodium borohydride (13.0mg, 0.344mmol) in one portion. The mixture was stirred at 20°C for 72 h before addition of water (5cm³) and extraction with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 1:1) to afford 1-benzyl-6-hydroxy-7-hydroxymethyl-3-phenyl-hexahydropyrrolo[1,2-*a*]imidazol-5-one **275** as an unstable colourless gum (14.0mg, 19%) δ_{H} (CDCl₃; 300MHz) 2.51 (t, 1H, *J* 9.6Hz, PhCHCHHN), 2.61 (m, 1H, CHCH₂OH), 3.36 (d, 1H, *J* 13.0Hz, NCHHPh), 3.64 (dd, 1H, *J* 7.5, 9.6Hz, PhCHCHHN), 3.91 (d, 2H, *J* 5.3Hz, CHCH₂OH), 4.21 (d, 1H, *J* 13.0Hz, NCHHPh), 4.27 (d, 1H, *J* 4.6Hz, NCHCHCH₂OH), 4.61 (d, 1H, *J* 9.2Hz, CHOH), 5.04 (dd, 1H, *J* 7.5, 9.6Hz, PhCHNC=O), 7.19-7.34 (m, 10H, Ar-H); %) δ_{C} (CDCl₃; 75MHz) 53.5 (CHCH₂OH), 56.1 (CHCH₂OH), 57.1 (PhCHNC=O), 61.5 & 62.2 (PhCHCH₂N & NCH₂Ph), 73.4 (CHOH), 79.9

(NCHCHCH₂OH), 125.7, 125.9, 127.6, 128.5, 128.7 & 129.0 (Ar-CH), 137.5 & 139.8 (Ar-C), 175.8 (C=O).

Attempted preparation of 1-benzyl-6-hydroxy-7-methoxycarbonyl-3-phenyltetrahydropyrrolo[1,2-*a*]imidazole (278)

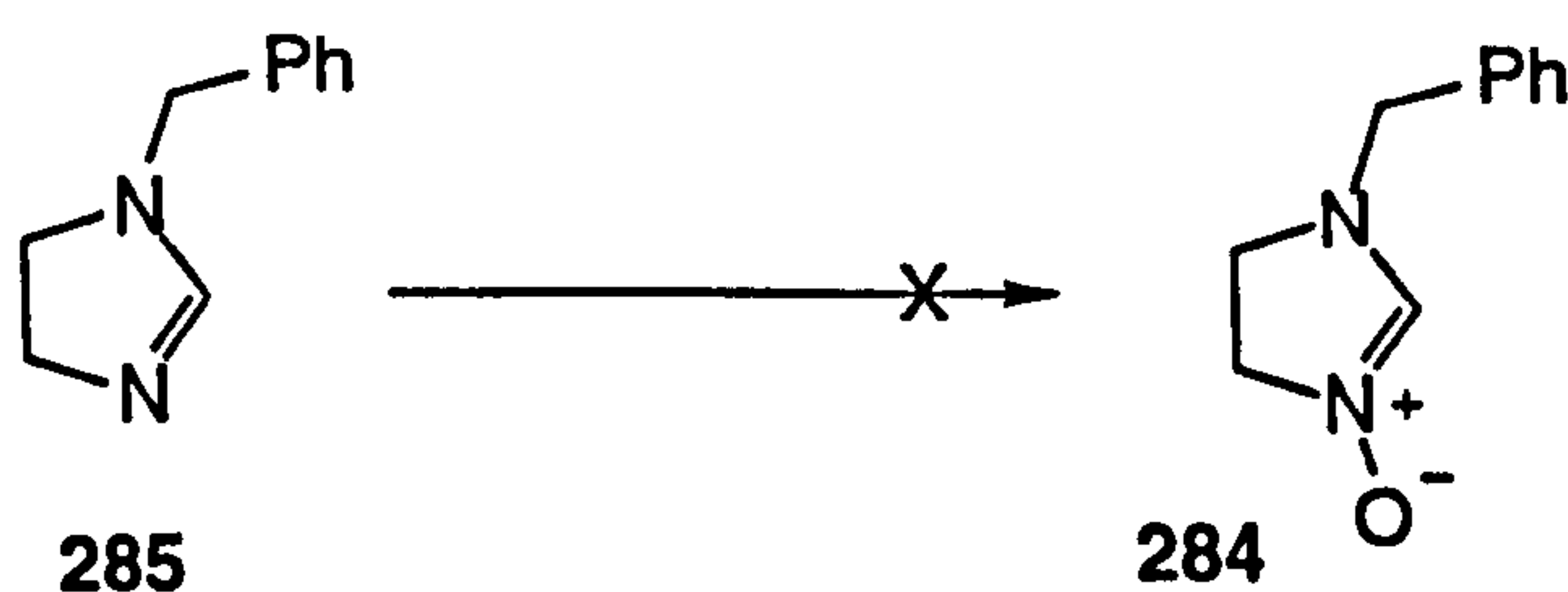


A solution of the methyl hydroxy lactam **271** (100mg, 0.273mmol) in distilled anhydrous THF (5cm³) under an atmosphere of nitrogen was treated with borane-THF complex (1M solution in THF, 2.73cm³, 2.73mmol) in one portion and heated under reflux for 18 h. The solution was cooled to 20°C and carefully treated with aqueous HCl (6M; 10cm³) and stirred at 20°C for 1 h. This solution was then basified with aqueous NaOH (10M) and extracted with ether (3 x 30cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure before purification of the residue by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v). The isolated product was not the title compound but 1-benzyl-7-methoxycarbonyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-*a*]imidazole **279** (20.0mg, 23%); δ_{H} (CDCl₃; 300MHz) 3.27 (dd, 1H, *J* 5.6, 12.7Hz, PhCHCHHN), 3.35 (dd, 1H, *J* 8.8, 12.7Hz, PhCHCHHN), 3.77 (s, 3H, CO₂CH₃), 3.81 (s, 2H, NCH₂Ph), 5.26 (dd, 1H, *J* 5.6, 8.8Hz, PhCHCH₂N), 6.61 & 6.70 (each m, 1H,

NCH=CH), 7.10 & 7.24-7.58 (m, 10H, Ar-H); δ_c (CDCl₃; 75MHz) 51.0 (CO₂CH₃), 52.7 (PhCHCH₂N), 53.5 (NCH₂Ph), 63.7 (PhCHCH₂N), 110.4 (NCH=CH), 121.1 (NCH=CH), 116.2, 125.0, 126.5, 127.3, 128.1, 128.3, 128.5, 128.9, 138.9 & 139.3 (Ar-C, Ar-CH & NC=CCO₂CH₃), 165.2 (CO₂CH₃).

This experiment was then repeated at 20°C for 18 h but afforded only an intractable mixture of products. Similarly, using the methodology of Fleet *et al.*,³⁰⁰ a solution of the lactam (100mg, 0.273mmol) in distilled anhydrous THF (10cm³) under an atmosphere of nitrogen was treated with borane-dimethyl sulphide complex (2M solution in THF, 0.55cm³, 1.09mmol) in one portion. After stirring at 20°C for 18 h, the solution was evaporated to return a mixture of the starting material **271** and a trace of the pyrroloimidazole **279**.

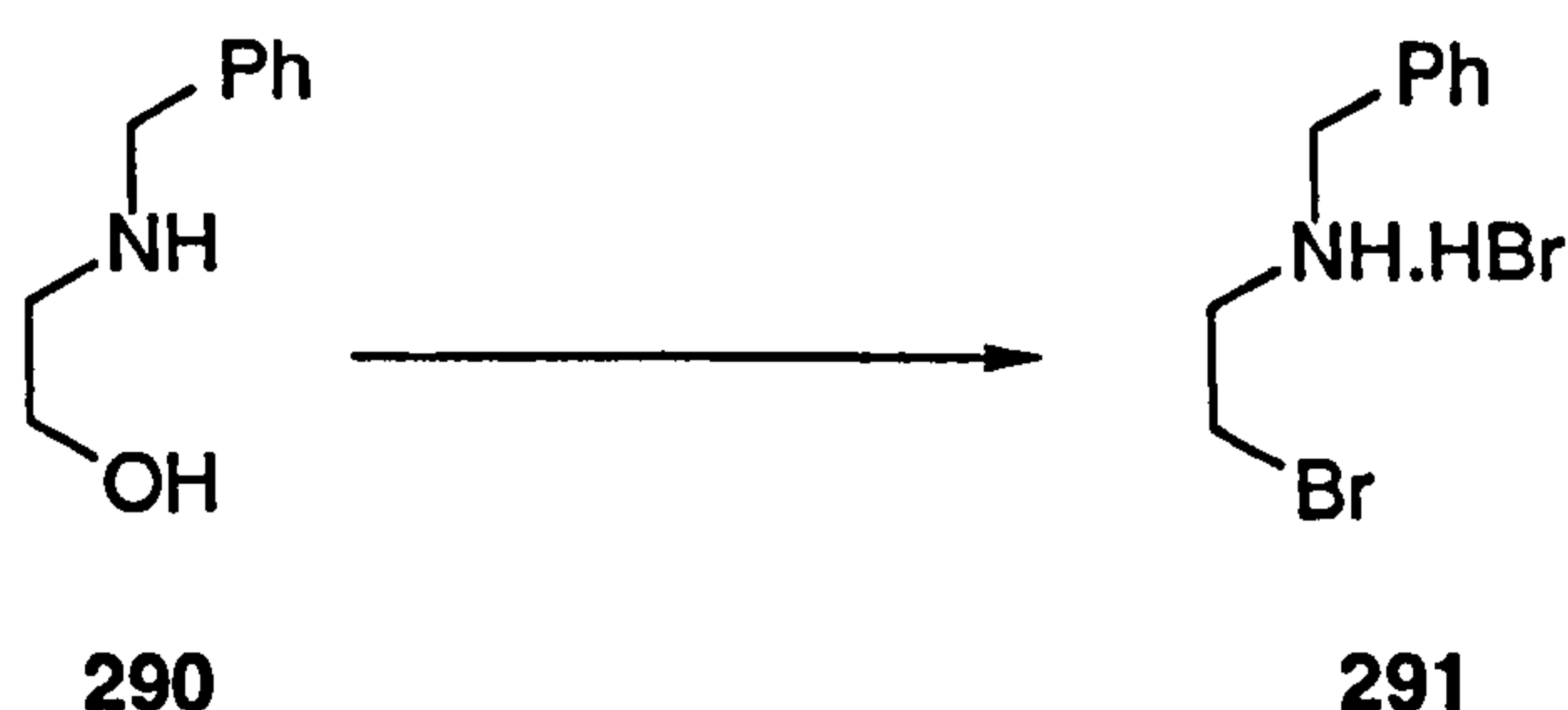
Attempted preparation of 3-benzyl-4,5-dihydroimidazole-1-oxide (**284**)



1-Benzyl-4,5-dihydroimidazole **285** (0.500g, 3.12mmol), prepared according to the published procedure,³²⁹ was treated with glacial acetic acid (1.85cm³) and aqueous hydrogen peroxide solution (27% w/v; 1.90cm³) and the mixture heated to reflux for 18 h. The cooled solution was concentrated under reduced pressure and made basic with sodium carbonate. The solution was extracted with chloroform (3 x 30cm³) and the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure. The residue was found to contain none of the desired material.

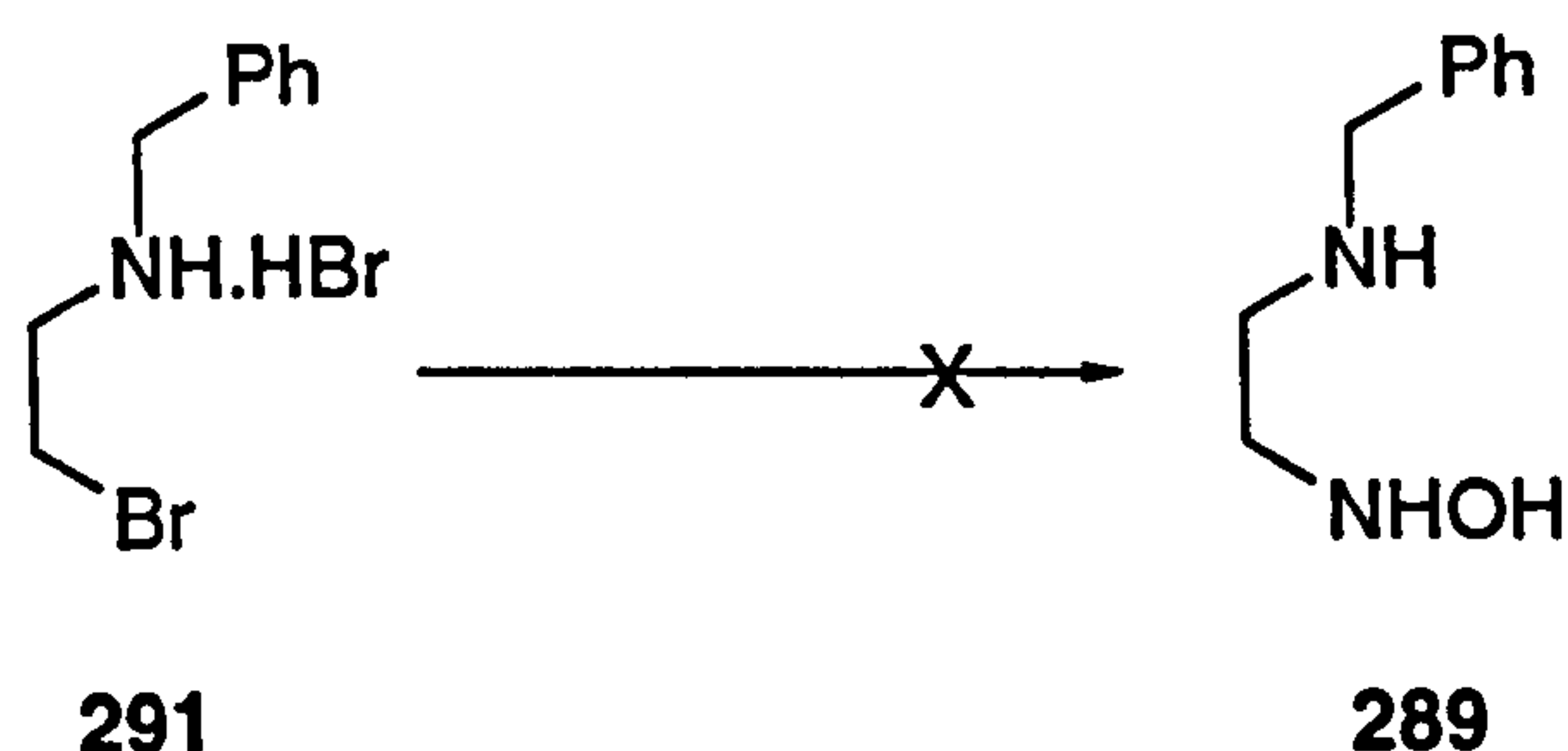
A solution of **285** (1.00g, 61.7mmol) in dry ether (100cm³) under nitrogen was treated with a solution of *m*CPBA (10.7g, 30.9mmol) in dry ether (100cm³) and stirred at 20°C for 24 h. The mixture was treated with aqueous sodium carbonate (10% w/v, 100cm³) and the ether layer removed. The aqueous layer was saturated with sodium chloride before extraction with ethyl acetate (3 x 100cm³). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure but afforded none of the desired material.

N-Benzyl-2-bromoethylamine hydrobromide (291)



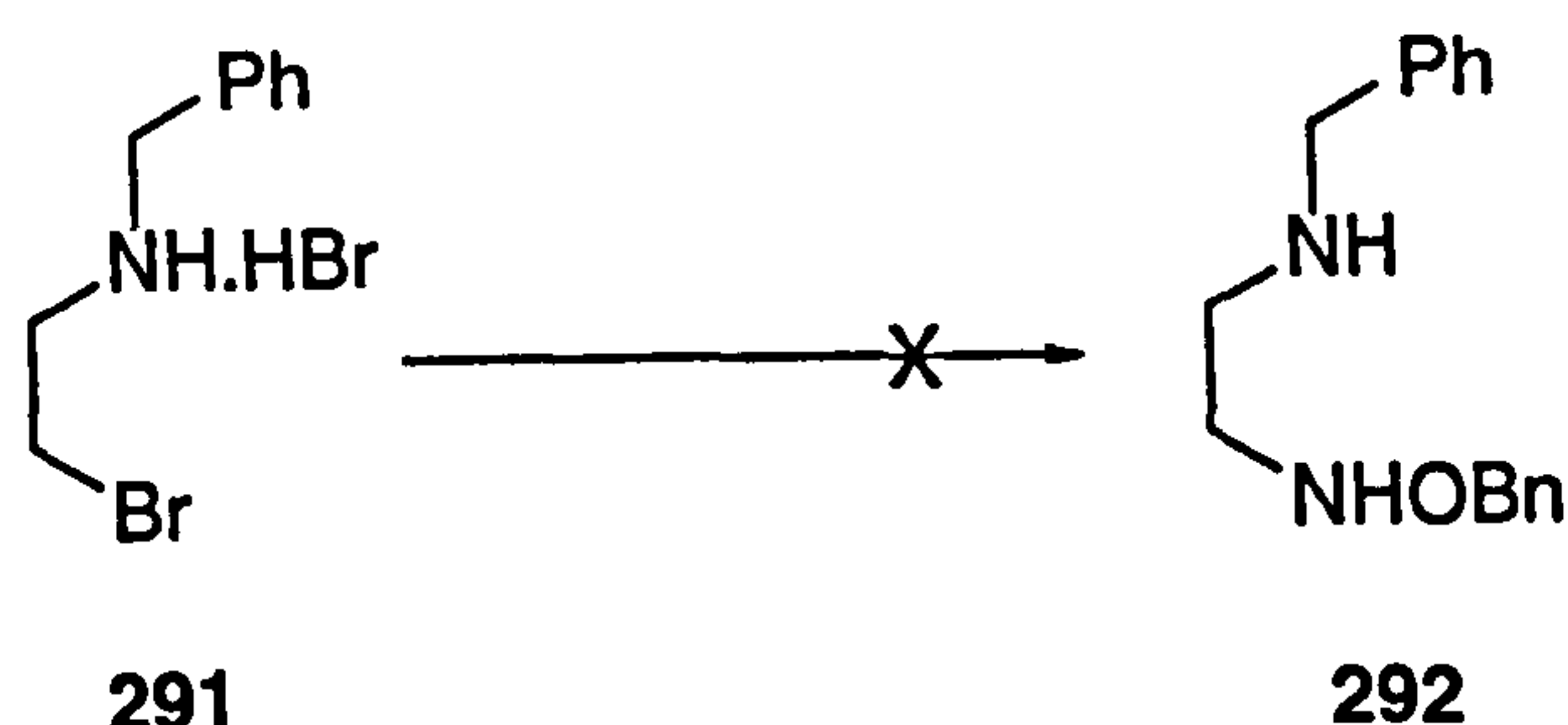
A mixture of N-benzylethanolamine **290** (5.00g, 33.1mmol) and aqueous HBr (48% w/v; 12cm³) was heated to 130°C for 4 h, during which time water (7cm³) was allowed to distill off. Upon cooling, a brown solid formed which was washed with ether / ethyl acetate (1:1 v/v; 50cm³) then DCM (50cm³) before drying under reduced pressure. The resultant off-white solid was shown to be a 3.9:1 mixture of the desired product **291** and N-benzylethanolamine **290** by ¹H NMR (2.30g of mixture corresponds to 1.83g of **291**, 19%); δ_{H} (CDCl₃; 400MHz) 3.27 (t, 2H, CH₂NH₂⁺, *J* 7.0Hz), 3.73 (t, 2H, CH₂Br, *J* 7.0Hz), 4.22 (s, 2H, NH₂⁺CH₂Ph), 7.43 (m, 3H) & 7.53 (m, 2H, Ar-H); δ_{C} (CDCl₃; 100MHz) 26.7 (CH₂Br), 47.6 & 50.0 (CH₂NH₂⁺CH₂Ph).

Attempted preparation of N-(2-benzylaminoethyl)hydroxylamine (289)



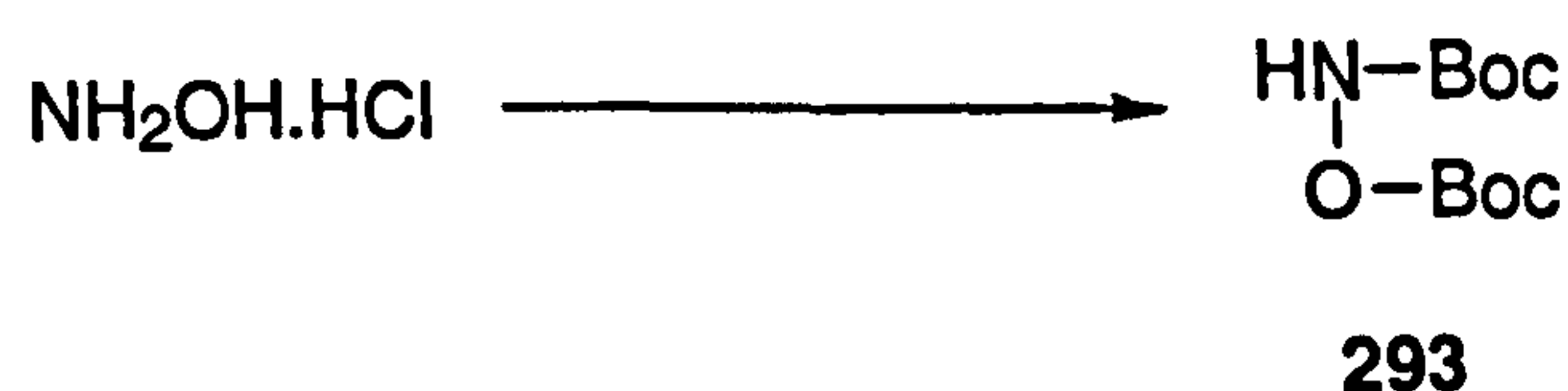
A solution of N-benzyl-2-bromoethylamine hydrobromide **291** from the previous preparation (0.500g, 70% pure, ≈ 1.19 mmol) in absolute ethanol (10cm³) was treated with hydroxylamine hydrochloride (0.130g, 1.86mmol) and triethylamine (0.730cm³, 5.24mmol). The solution was heated under reflux for 2 h before the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) but none of the desired product was isolated. This procedure was repeated with overnight heating at reflux in THF, and in ethanol with 5 equivalents of hydroxylamine hydrochloride and 6 of triethylamine but without success.

Attempted preparation of O-benzyl-N-(2-benzylaminoethyl)hydroxylamine (292)



A solution of **291** from the preparation described above (0.500g, 70% pure, $\approx 1.18\text{mmol}$), triethylamine (0.730cm^3 , 5.24mmol) and O-benzylhydroxylamine hydrochloride (0.280g, 1.86mmol) was treated as described in the attempted synthesis of **289** above. After 72 h of heating at reflux, none of the desired material was isolated. This procedure was repeated with DMF as the solvent, but without success.

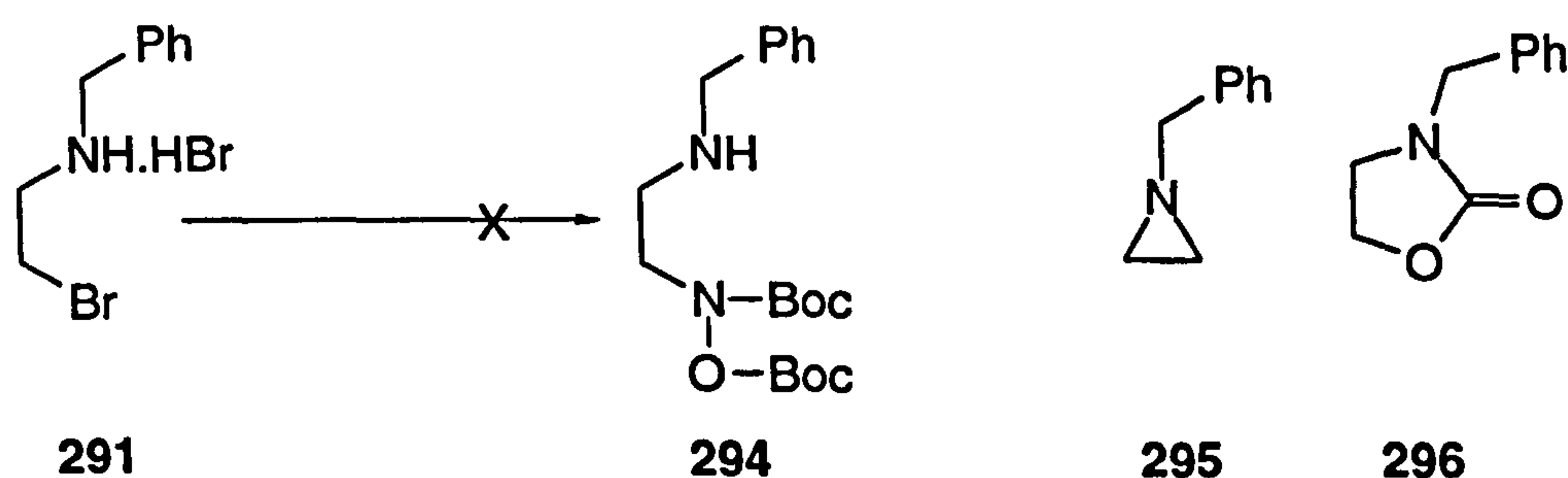
N,O-Bis-*tert*-Butoxycarbonylhydroxylamine (293)



According to the method of Whiting and Baillie,³¹³ a mixture of hydroxylamine hydrochloride (2.00g, 28.8mmol) and sodium carbonate (5.17g, 37.4mmol) in water (20cm^3) at 30°C was treated portionwise with di-*tert*-butyl dicarbonate (13.2g, 60.4mmol). After 2 h, the mixture was cooled to 20°C before stirring for 18 h. After extraction with toluene ($3 \times 30\text{cm}^3$), the organic phase was dried (MgSO_4), filtered and evaporated to yield

the title compound **293** as a white crystalline solid (3.61g, 54%), mp 66-67°C (lit.³¹³, 67-71°C); δ_{H} (CDCl₃; 400MHz) 1.50 (s, 9H) & 1.52 (each s, 9H, 2 x C(CH₃)₃), 7.61(br s, 1H, NH); δ_{C} (CDCl₃; 100MHz) 27.5 & 28.0 (2 x C(CH₃)₃), 83.1 & 85.4 (2 x C(CH₃)₃), 153.6 & 155.7 (2 x C=O); ν_{max} (KBr) /cm⁻¹ 3274, 1797, 1740, 1720, 1242, 1156, 1126; m/z 234 (MH⁺, 4%), 231 (12%), 172 (14%), 116 (100%), 72 (15%), 57 (8%).

Attempted preparation of N-(2-benzylaminoethyl)-N,O-bis-tert-butoxycarbonyl-hydroxylamine (294)

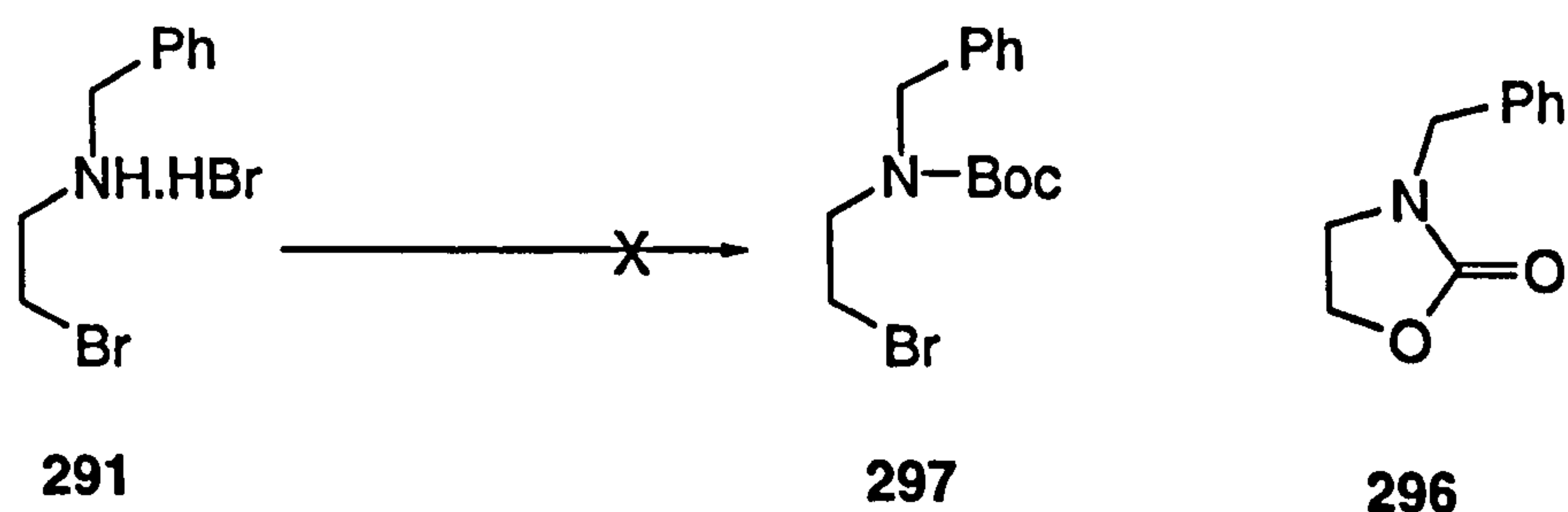


A stirred solution of N,O-bis-tert-butoxycarbonylhydroxylamine **293** (0.710g, 3.04mmol) in DMF (15cm³) was treated with potassium carbonate (1.00g, 7.23mmol) and N-2-bromo-benzylethylamine hydrobromide **291** (1.00g, 70% pure, 2.36mmol). After 18 h at 20°C, the mixture was diluted with water and toluene (30cm³ each). The organic layer was separated, dried (MgSO₄) and filtered before evaporation under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) but the title compound **294** was not isolated. It was possible to isolate and characterise three compounds from this reaction: recovered N,O-bis-tert-butoxycarbonylhydroxylamine **293** (0.480g, 67% of total quantity used), N-benzylaziridine **295** (0.130g, 42% based on bromide used)

and 3-benzyl-2-oxazolidinone **296** (0.120g, 28% based on bromide); **3-Benzyl-2-oxazolidinone 296** : δ_{H} (CDCl_3 ; 400MHz) 3.42 (t, 2H, J 8.0Hz, CH_2O), 4.31 (t, 2H, J 8.0Hz, $\text{CH}_2\text{NCH}_2\text{Ph}$), 4.43 (s, 2H, NCH_2Ph), 7.27-7.36 (m, 5H, Ar-H); $^{330}\delta_{\text{C}}$ (CDCl_3 ; 100MHz) 43.8 ($\text{CH}_2\text{NCH}_2\text{Ph}$), 48.2 (CH_2O), 61.6 (NCH_2Ph), 127.8, 127.9 & 129.0 (Ar-CH), 135.6 (Ar-C), 158.4 ($\text{C}=\text{O}$); m/z 177 (M^+ , 31%), 176 (30%), 132 (15%), 105 (26%), 104 (100%), 91 (99%); **Benzylaziridine 285**; the isolated material had data consistent with that for an independently prepared sample described in a following procedure.

The above method was used with THF as the solvent in place of DMF, but without success. This was combined with replacement of the potassium carbonate by sodium hydride, but none of the desired material was observed.

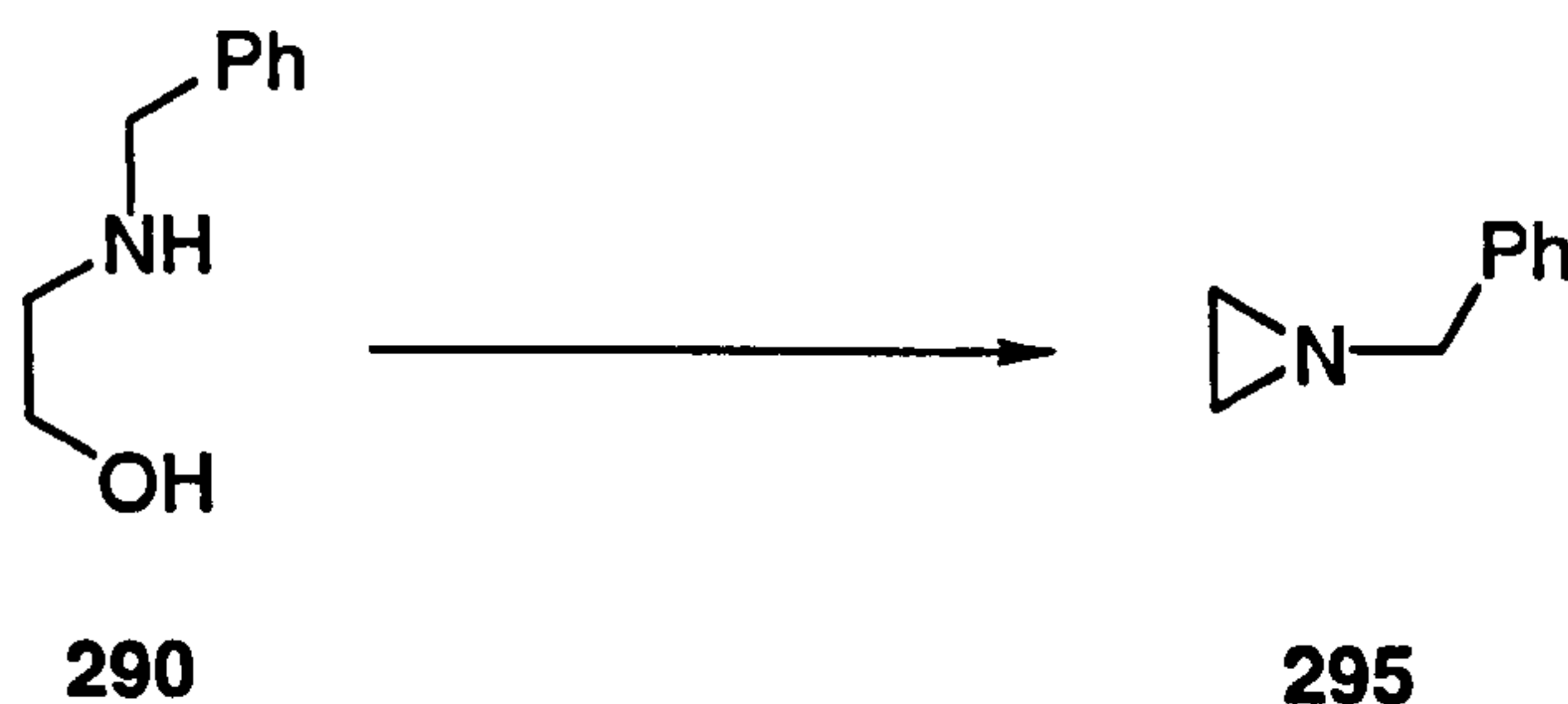
Attempted preparation of N-benzyl-2-bromo-N-*tert*-butoxycarbonyl-ethanamine (297)



A stirred solution of N-benzyl-2-bromoethanamine hydrobromide **291** from the earlier preparation (1.00g, 50% pure, 0.560g of **291**, 1.90mmol) in water (20cm³) was treated with sodium carbonate (1.72g, 16.2mmol) and di-*tert*-butyl dicarbonate (2.50g, 7.12mmol) and stirred for 48h at room temperature. The solution was extracted with toluene (3 x 30cm³), dried (MgSO_4), filtered and evaporated to dryness under reduced pressure

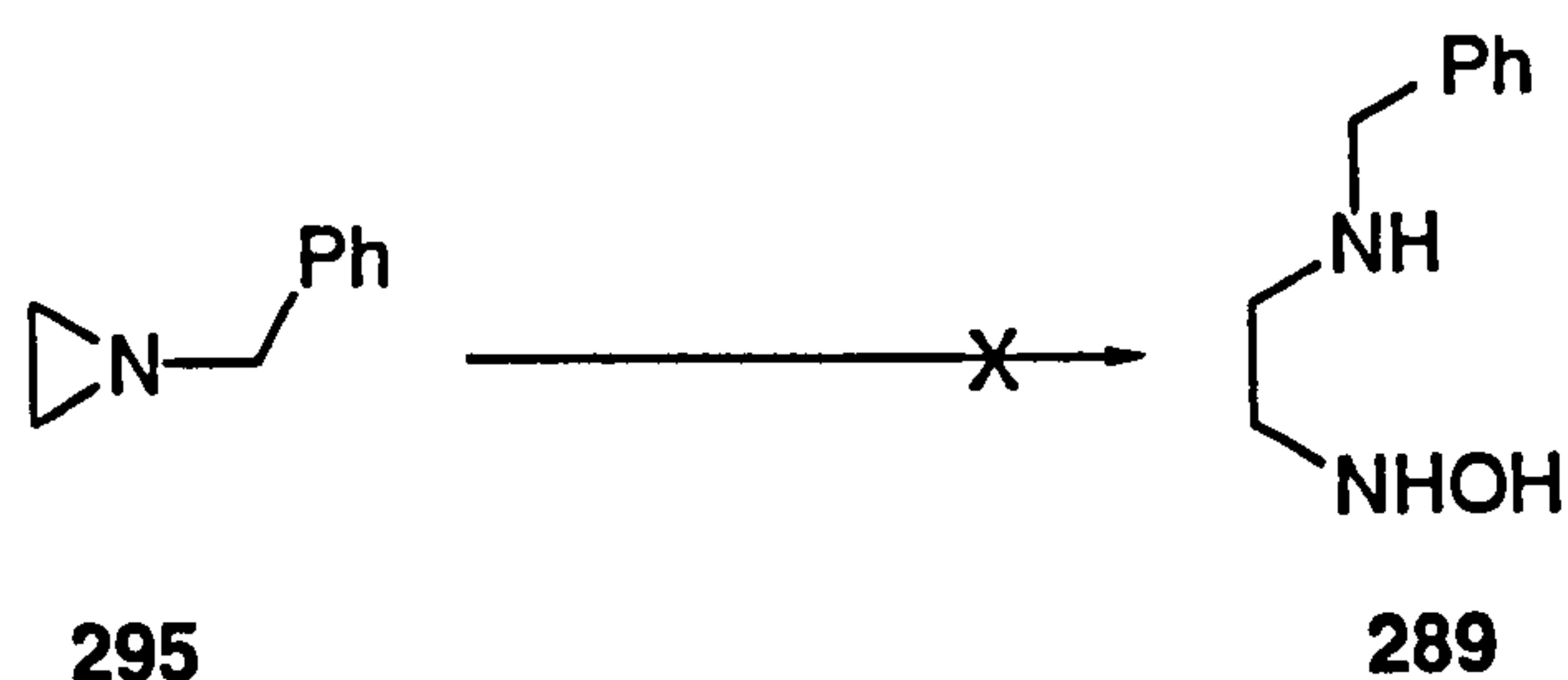
before purification of the residue by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v). The only isolated materials were recovered di-*tert*-butyl dicarbonate (20% of initial quantity) and 3-benzyl-2-oxazolidinone **296** (30% based on bromo amine **291**).

N-Benzylaziridine (**295**)



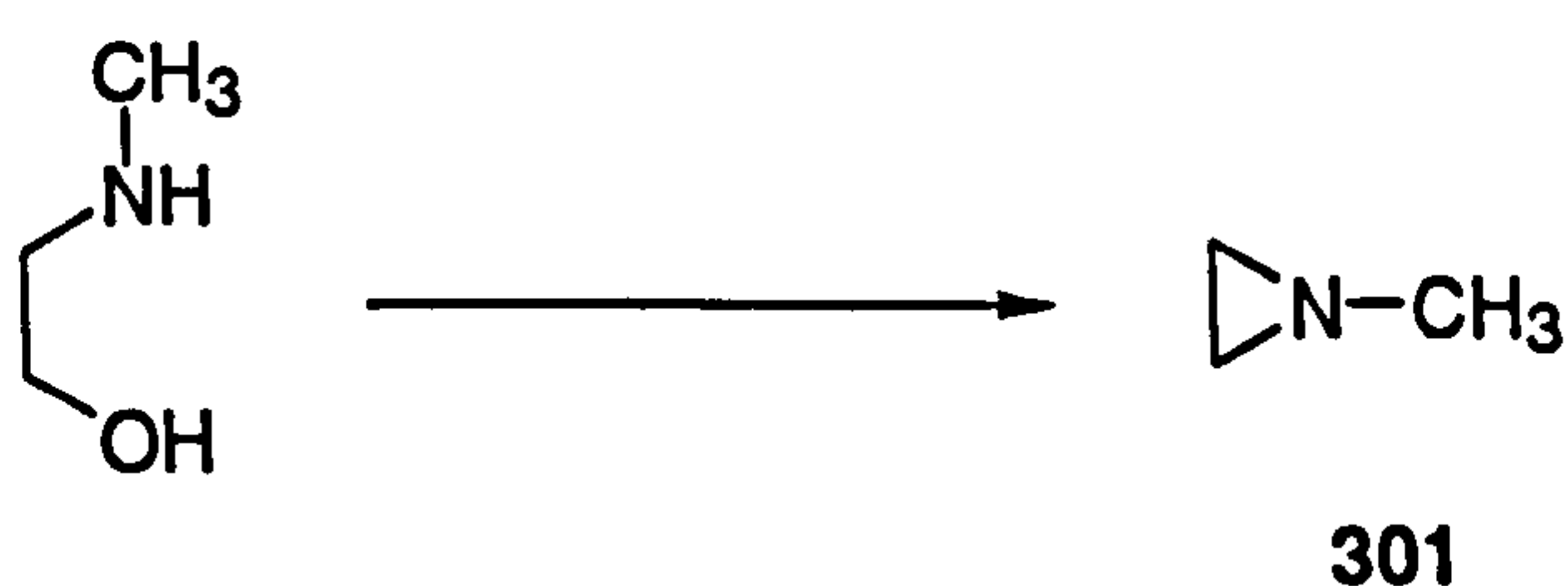
A solution of N-benzylethanamine **290** (2.00g, 13.2mmol) in toluene (30cm³) was treated with sulfur trioxide-trimethylamine complex (2.20g, 15.8mmol) and the mixture heated under reflux for 2 h. After cooling to 60°C and addition of aqueous NaOH (10M; 5cm³), the solution was heated under reflux for a further 2 h. The cooled solution was then washed with water (30cm³) and the organic phase dried (MgSO₄), filtered and evaporated under reduced pressure to give the title compound **295** as a clear oil (0.500g, 30%). This material was further purified by distillation, bp 64°C, 6mmHg, lit.,³³¹ 80-82°C, 10mmHg; δ_{H} (CDCl₃; 400MHz) 1.30 & 1.85 (each m*, 2H, CH₂CH₂), 3.40 (s, 2H, NCH₂Ph), 7.26-7.38 (m, 5H, Ar-H), δ_{C} (CDCl₃; 400MHz) 27.5 (CH₂CH₂), 65.3 (NCH₂Ph), 127.0, 128.0, 128.3 (Ar-CH), 139.3 (Ar-C.); [m* : The ring protons are "triplets" with inverted peak ratios, i.e. 2:1:2³³²⁻³³⁴].

Attempted preparation of N-(2-benzylaminoethyl)hydroxylamine (289)



According to the reported procedures,^{314,315} a mixture of hydroxylamine hydrochloride (0.130g, 1.88mmol), triethylamine (0.260cm³, 1.88cm³) and ammonium chloride (5.0mg, 93.5μmol) in methanol (2cm³) was treated with N-benzylaziridine **295** (0.250g, 1.88mmol) and stirred vigorously for 18 h. The solvent was evaporated under reduced pressure to give an intractable mixture of unidentifiable products.

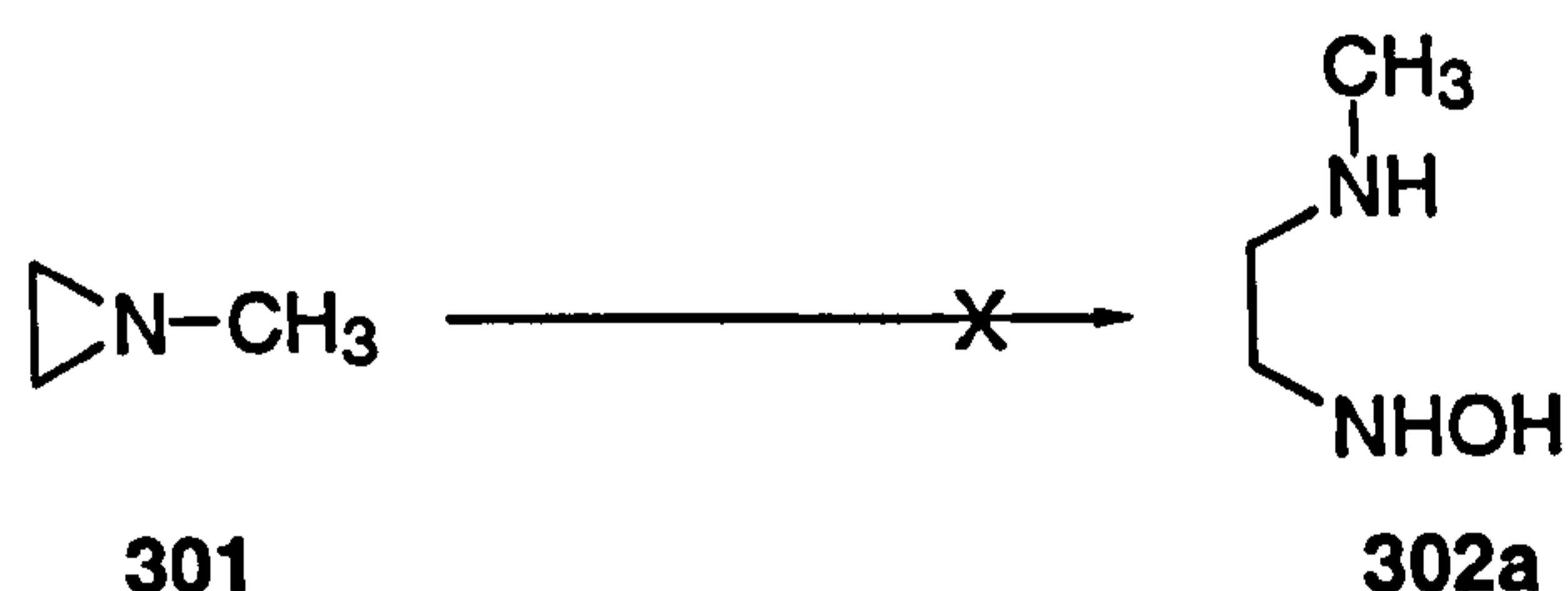
N-Methylaziridine (301)



To stirred N-methylethanolamine (5.00g, 66.6mmol) was added chlorosulfonic acid (4.43cm³, 66.6mmol) at 0°C with violent evolution of gas. The resultant viscous oil was heated to 150°C under vacuum (20mmHg) for 2 h. The residue was cooled to 20°C and dissolved in water (10cm³) before addition of aqueous KOH (20M; 20cm³). The solution was heated to 100°C to distill off a clear oil consisting of a 1:1 mixture of N-

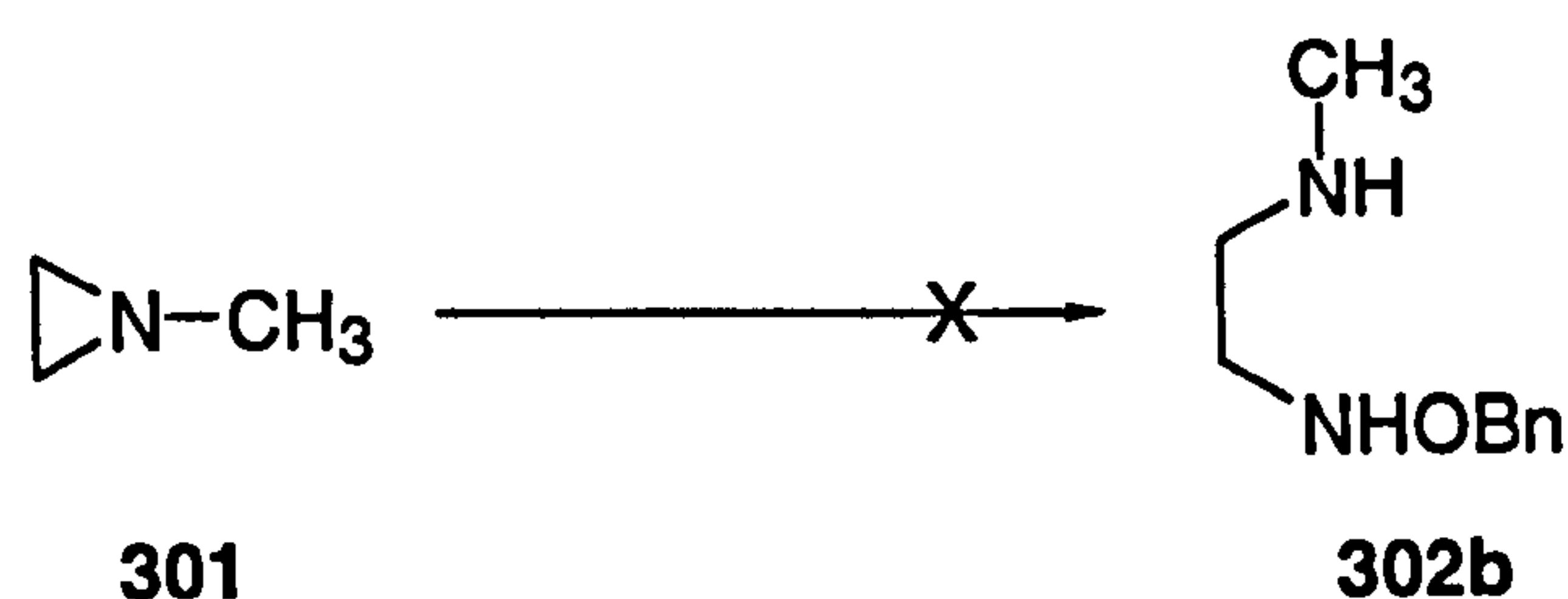
methylethanolamine and the title compound **301**, bp 82-86°C (lit.,³³² 24-25°C); δ_{H} (CDCl_3 ; 400MHz) 1.03 & 1.70 (each m*, 2H, $\text{CH}_2\text{CH}_2\text{NCH}_3$), 2.27 (d, 3H, NCH_3); δ_{C} (CDCl_3 ; 400MHz) 28.4 ($\text{CH}_2\text{CH}_2\text{NCH}_3$), 48.3 (NCH_3); [m* : The ring protons are "triplets" with inverted peak ratios, i.e. 2:1:2³³²⁻³³⁴].

Attempted preparation of N-(2-methylaminoethyl)hydroxylamine (302a)



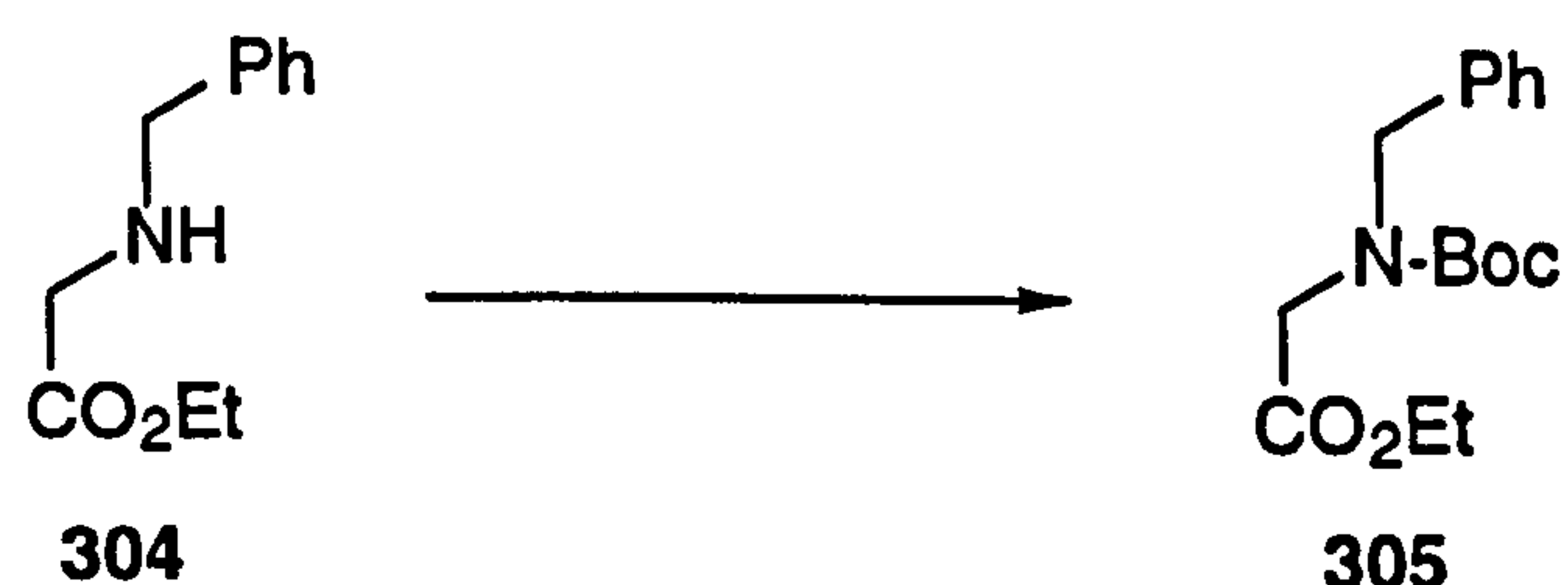
A mixture of hydroxylamine hydrochloride (0.500g, 7.20mmol), triethylamine (1.01cm³, 7.25mmol) and ammonium chloride (8.0mg, 0.150mmol) in methanol (5cm³) was treated with N-methylaziridine **301** (0.180g, 3.15mmol) and the mixture stirred vigorously for 18 h. The solvent was evaporated under reduced pressure to give an intractable mixture of unidentifiable products.

Attempted preparation of O-benzyl-N-(2-methylaminoethyl)hydroxylamine (302b)



A mixture of O-benzylhydroxylamine hydrochloride (2.79g, 17.5mmol), triethylamine (2.44cm³, 17.5mmol) and ammonium chloride (47.0mg, 0.879mmol) in methanol (10cm³) was treated with N-methylaziridine **301** (1.00g, 17.5mmol) and the mixture stirred vigorously for 48 h. The solvent was evaporated under reduced pressure to give an intractable mixture of unidentifiable products.

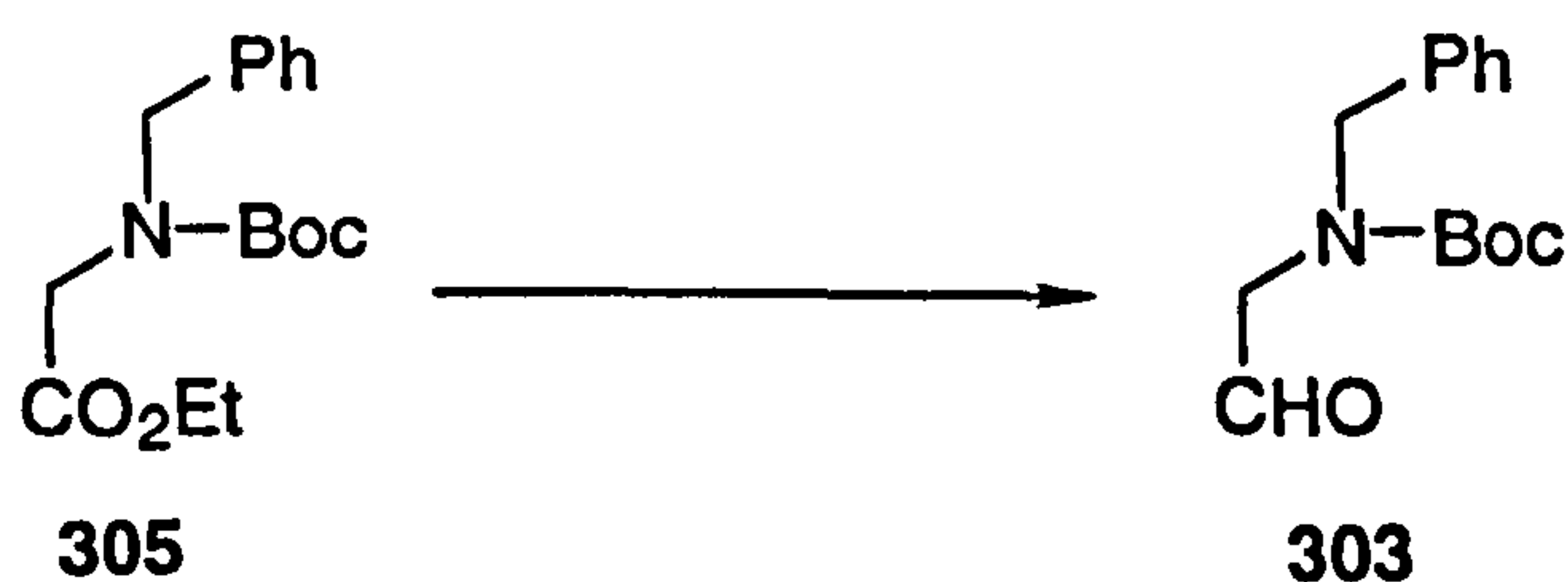
N-Benzyl-N-*tert*-butoxycarbonylglycine ethyl ester (305)



A stirred solution of N-benzylglycine ethyl ester **304** (5.00g, 25.9mmol) in DCM (100cm³) at 0°C under an atmosphere of nitrogen was treated with triethylamine (7.20cm³, 51.8mmol) and a solution of di-*tert*-butyl dicarbonate (6.20g, 28.5mmol) in DCM (50cm³). After warming to 20°C overnight, the solution was washed with aqueous citric acid (1M; 5 x

20cm³) and the organic phase dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 1:1 v/v) to afford the *title compound* **305** as a white solid (5.80g, 76%) which was seen to exist as a pair of carbamate rotamers by NMR; δ_{H} (CDCl₃; 400MHz) 1.26 (m, 6H, 2 x OCH₂CH₃), 1.48 (2 x br s, 18H, C(CH₃)₃), 3.78 & 3.92 (each s, 2H, 2 x NCH₂CO₂CH₂CH₃), 4.18 (m, 4H, 2 x OCH₂CH₃), 4.52 & 4.55 (each s, 2H, 2 x NCH₂Ph), 7.22-7.35 (m, 20H, Ar-H); δ_{C} (CDCl₃; 100MHz) 14.1 & 14.2 (OCH₂CH₃), 28.2 & 28.3 (C(CH₃)₃), 47.7 & 48.1, 51.0 & 51.5 (NCH₂CO₂CH₂CH₃ & NCH₂Ph), 60.9 & 61.0 (OCH₂CH₃), 80.4 & 80.6 (C(CH₃)₃), 2 x 127.4, 127.5, 128.1, 2 x 128.5 (Ar-CH), 137.6 & 137.3 (Ar-C), 155.6 & 155.8 (NC=O), 169.9 & 170.0 (CO₂CH₂CH₃).

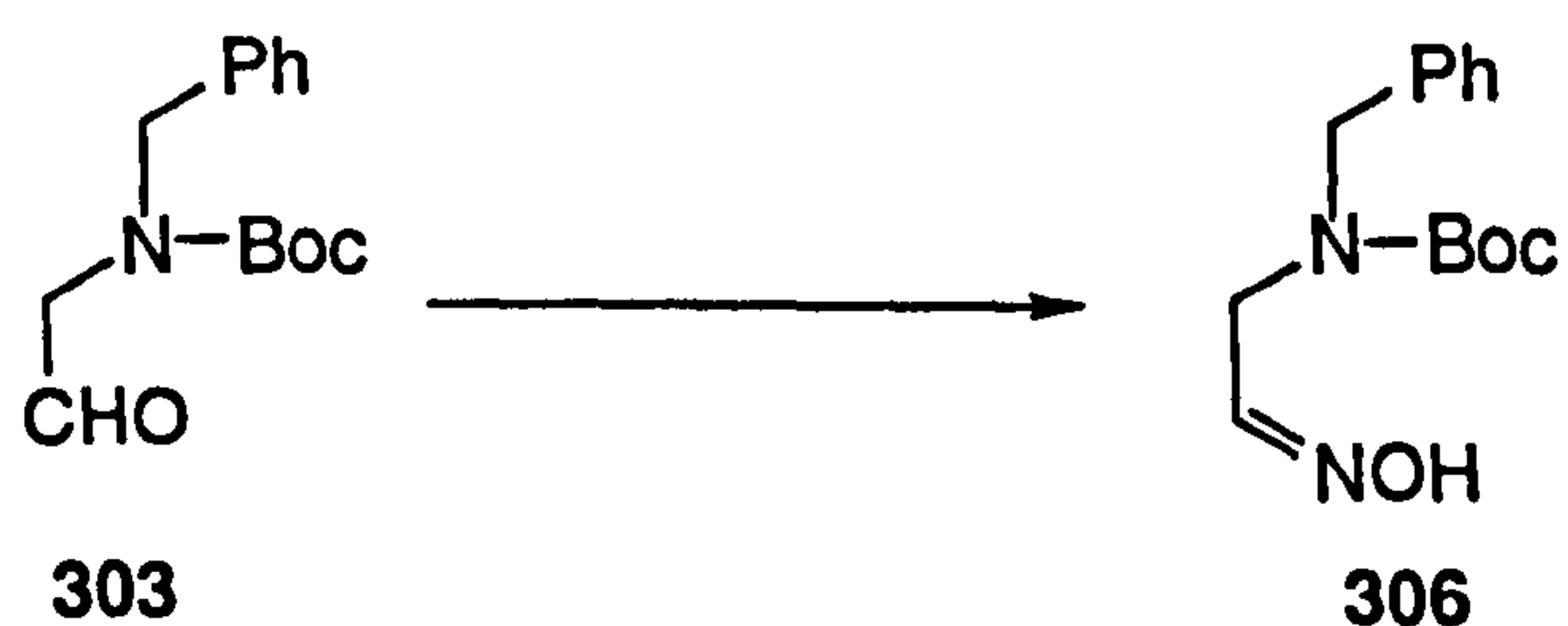
N-Benzyl-N-*tert*-butoxycarbonylglycinal (**303**)



A solution of N-benzyl-N-*tert*-butoxycarbonylglycine ethyl ester **305** (3.29g, 11.2mmol) in anhydrous toluene (80cm³) at -78°C was treated with DIBAL (1M soln. in toluene, 28.0cm³, 28.0mmol) over 25 min. After 1.5 h the reaction was quenched with methanol (10cm³) and poured into a solution of Rochelle's salt (potassium sodium tartrate tetrahydrate) (215g, 0.719mol) in water (500cm³) along with a little toluene present to maintain stirring of the thick emulsion that formed. After vigorous stirring for 1.5 h, two

separate phases had formed. The organic phase was separated and the aqueous further extracted with ether (3 x 150cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated to dryness under reduced pressure. Column chromatography of the residue gave the *title compound 303* as a clear, mobile oil (2.30g, 82%) containing a mixture of carbamate rotamers; δ_{H} (CDCl₃; 400MHz) 1.46 & 1.49 (each s, 9H, 2 x C(CH₃)₃), 3.79 & 3.83 (each s, 2H, 2 x NCH₂CHO), 3.49 & 3.52 (each s, 2H, 2 x NCH₂Ph), 7.18-7.35(m, 20H, Ar-H), 9.40 & 9.50 (each s, 1H, 2 x CHO); δ_{C} (CDCl₃; 400MHz) 28.2 & 28.3 (C(CH₃)₃), 51.5, 52.0, 56.4 x 2 (2 x NCH₂CHO & 2 x NCH₂Ph), 81.1 (2 x C(CH₃)₃), 127.6, 127.7, 127.8, 128.1, 128.6 & 128.8 (Ar-CH), 137.1 & 137.3 (Ar-C), 198.8 & 198.9 (2 x CHO); m/z 250 (MH⁺, 18%), 220 (33%), 194 (100%), 164 (28%), 150 (41%), 120 (49%), 91 (100%), 57 (99%).

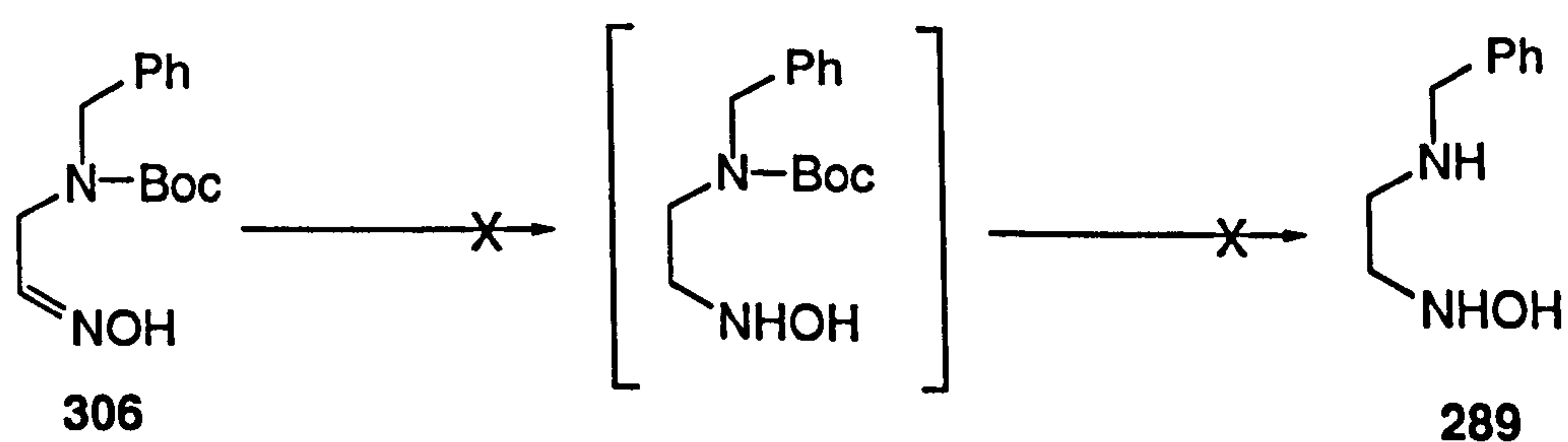
N-Benzyl-N-*tert*-butoxycarbonylglycinaldoxime (306)



A solution of sodium acetate (6.80g, 82.9mmol) and hydroxylamine hydrochloride (3.40g, 48.9mmol) in a mixture of water (20cm³) and ethanol (10cm³) was added to N-benzyl-N-*tert*-butoxycarbonylglycinal **303** (1.70g, 6.82mmol) and heated to 60°C for 2 h with vigorous stirring. The solution was cooled to 20°C and extracted with DCM (3 x 150cm³). The organics were dried (MgSO₄), filtered, evaporated under reduced pressure and

the residue purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the *title compound 306* as a white solid (0.885g, 49%) tentatively assigned as a mixture of oxime isomers and carbamate rotamers; δ_{H} (d₆-DMSO; 400MHz) 1.40 (br s, 9H, C(CH₃)₃), 3.79, 3.86, 3.92 & 3.97 (each br s, 0.5H, NCH₂C=NOH), 4.35 & 4.40 (each s, 1H, NCH₂Ph), 7.20-7.36 (Ar-H); δ_{C} (CDCl₃; 100MHz) 28.2, 28.4 & 2 x 28.6 (C(CH₃)₃), 42.1, 42.3, 44.9, 45.1, 49.8, 50.1, 51.1 & 51.7 (NCH₂C=NOH & NCH₂Ph), 80.7 (C(CH₃)₃), 127.4, 127.5, 128.8, 128.0, 128.4, 2 x 128.6, 2 x & 128.9 (Ar-CH), 137.6 (Ar-C), 147.5 & 147.8 (CH=NOH), 150.2, 150.5, 150.7, 155.5 & 155.6 (C=O); *m/z* 265 (MH, 3%), 209 (37%), 191 (16%), 165 (38%), 163 (22%), 150 (60%), 147 (57%), 120 (30%), 106 (64%), 91 (100%).

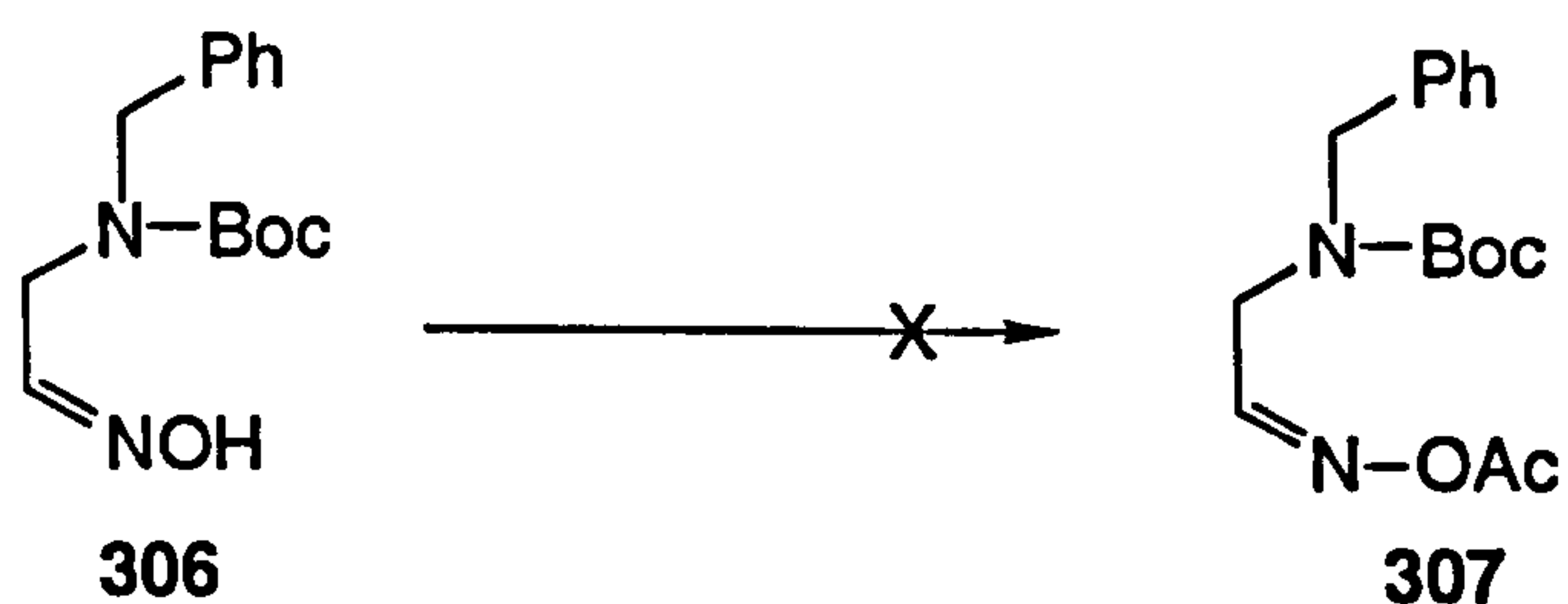
Attempted preparation of N-(2-benzylaminoethyl)hydroxylamine (289)



A solution of N-benzyl-N-*tert*-butoxycarbonylglycinaldoxime **306** (0.100g, 0.378mmol) in anhydrous THF (5cm³) was treated with borane-THF complex (1M solution in THF, 0.760cm³, 0.760mmol) at 20°C with stirring under an atmosphere of nitrogen. After 60 h, aqueous HCl (6M; 5cm³) was added dropwise with much evolution of gas and the solution stirred for a further hour before the solution was basified with solid KOH and extracted with DCM (3 x 30cm³). The organics were then dried (MgSO₄), filtered and

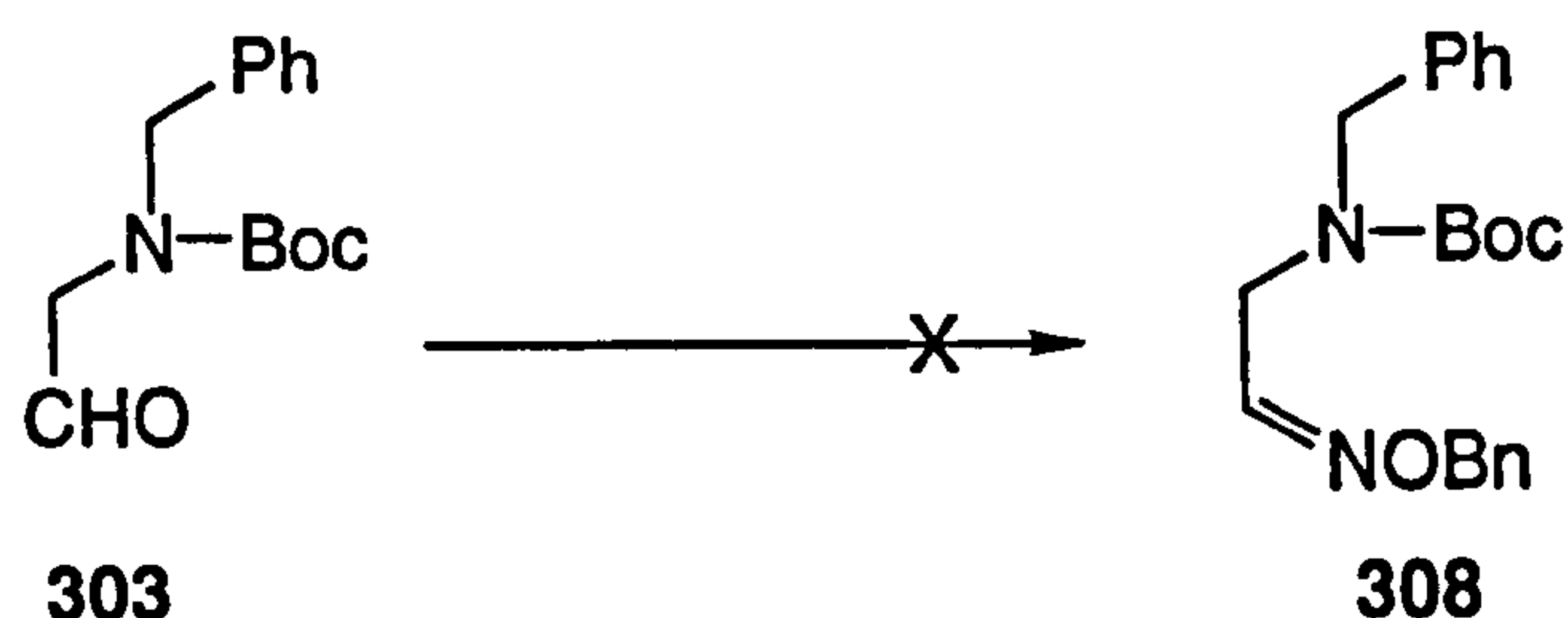
evaporated under reduced pressure to give a colourless film (40mg) from which none of the desired product could be identified.

Attempted preparation of N-benzyl-N-*tert*-butoxycarbonylglycinal O-acetyloxime (307)



A solution of N-benzyl-N-*tert*-butoxycarbonylglycinaldoxime **306** (0.480g, 1.82mmol) in pyridine (2cm³) was treated dropwise with acetyl chloride (0.140cm³, 2.00mmol) at 0°C and warmed to 20°C overnight. The solution was partitioned between ether (20cm³) and aqueous citric acid (1M; 20cm³) and the aqueous extracted with further ether (2 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to afford a yellow oil which did not yield the title compound after purification by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v).

Attempted preparation of N-benzyl-N-*tert*-butoxycarbonylglycinal O-benzyloxime (308)



According to the procedure described for the preparation of **306** above, aldehyde **303** (0.650g, 2.61mmol), O-benzylhydroxylamine hydrochloride (0.460g, 2.87mmol), sodium acetate (1.00g, 12.2mmol) and aqueous ethanol (1:1 v/v, 10cm³) were used in an attempt to synthesise **308**. However, after 18 h at 65°C, the crude reaction mixture did not afford the title compound after column chromatography (SiO₂, hexane:EtOAc 9:1 v/v).

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Appendix I

X-ray crystallographic data

Empirical formula	$C_{22}H_{24}N_2O_5$
Formula weight	396.43
Temperature	293 (2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	$a = 11.344 (2) \text{ Å}$ $b = 11.341 (2) \text{ Å}$ $c = 33.051 (7) \text{ Å}$
Volume	4252.1 (14) Å ³
Z	8
Density (calculated)	1.239 Mg/m ³
Absorption coefficient	0.726 mm ⁻¹
F (000)	1680
Crystal size	0.2 x 0.2 x 0.3 mm
θ range for data collection	4.73 to 55.00°
Index ranges	$-14 \leq h \leq 0, -14 \leq k \leq 0, -41 \leq l \leq 0$
Reflections collected	2637
Independent reflections	2637 [$R_{int} = 0.0000$]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2635 / 0 / 264
Goodness-of-fit on F^2	0.984
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.494, wR2 = 0.1296$
R indices (all data)	$R1 = 0.950, wR2 = 0.1532$
Largest diff. peak and hole	0.194 and -0.198 e.Å ⁻³

Crystal data and structure refinement for 227.

Empirical formula	$C_{24}H_{24}N_2O_3S$
Formula weight	420.51
Temperature	150 (2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$C2/c$
Unit cell dimensions	$a = 33.5981 (12) \text{ Å}$ $\alpha = 90^\circ$ $b = 14.6601 (5) \text{ Å}$ $\beta = 93.701 (2)^\circ$ $c = 8.5981 (3) \text{ Å}$ $\gamma = 90^\circ$
Volume	$4226.2 (3) \text{ Å}^3$
Z	2
Density (calculated)	1.322 Mg/m^3
Absorption coefficient	0.182 mm^{-1}
F (000)	1776
Crystal / size	Prism, colourless / $0.6 \times 0.075 \times 0.075 \text{ mm}$
θ range for data collection	2.78 to 25.99°
Limiting indices	$-41 \leq h \leq 41$, $-15 \leq k \leq 18$, $-10 \leq l \leq 10$
Reflections collected / unique	19011 / 4160 [$R_{\text{int}} = 0.0779$]
Refinement method	Full-matrix least-squares on F^2
Completeness to $\theta = 25.99^\circ$	96.5%
Data / restraints / parameters	4160 / 0 / 368
Goodness-of-fit on F^2	0.995
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0427$, $wR2 = 0.0963$
R indices (all data)	$R1 = 0.0861$, $wR2 = 0.1044$
Extinction coefficient	$0.0008 (3)$
Largest diff. peak and hole	0.253 and -0.368 e.Å^{-3}

Crystal data and structure refinement for **241**.

Empirical formula	$C_{21}H_{22}N_2O_4$
Formula weight	366.41
Temperature	150 (2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	$a = 5.7560 (10) \text{ Å}$ $\alpha = 85.58 (2)^\circ$ $b = 11.341 (2) \text{ Å}$ $\beta = 84.21 (2)^\circ$ $c = 33.051 (7) \text{ Å}$ $\gamma = 81.91 (2)^\circ$
Volume	935.9 (3) Å ³
Z	2
Density (calculated)	1.300 Mg/m ³
Absorption coefficient	0.091 mm ⁻¹
F (000)	388
Crystal size	0.6 x 0.075 x 0.075 mm
θ range for data collection	41.94 to 26.00°
Limiting indices	$-7 \leq h \leq 7$, $-13 \leq k \leq 13$, $-19 \leq l \leq 19$
Reflections collected / unique	11704 / 3535 [$R_{\text{int}} = 0.0756$]
Refinement method	Full-matrix least-squares on F^2
Completeness to $\theta = 26.00^\circ$	96.5%
Data / restraints / parameters	3535 / 0 / 246
Goodness-of-fit on F^2	0.880
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0499$, $wR2 = 0.1207$
R indices (all data)	$R1 = 0.0861$, $wR2 = 0.1465$
Largest diff. peak and hole	0.223 and -0.306 e.Å ⁻³

Crystal data and structure refinement for **265**.

Appendix II

HPLC conditions

HPLC Instrumentation and Conditions

Compounds **208**, **140a**, **126a** and **126b** were analysed using a Varian Vista Series 5000 Liquid Chromatograph, with a Kratos Spectraflow 757 Absorbance Detector and Chromjet Integrator. The column used was a Waters Symmetry C18 (internal dimensions 25cm x 4.6mm). The injection loop was 20 μ l and was filled with the sample solution (1 drop of reaction mixture in 4cm³ of eluent A). Eluent A : 9:1 water:acetonitrile + 0.1% TFA (v/v). Eluent B : 1:9 water:acetonitrile + 0.1% TFA (v/v). Gradient elution was employed, with initial eluent 100% A, raising to 90% B after 15 minutes and maintaining this eluent composition for a further 10 minutes. The flow rate throughout was 1cm³ per minute.

Compounds **165** and **187b** were isolated by preparative HPLC using a Waters Delta Prep 3000 instrument and Phenomenex Luna 10 C₁₈ (2) column (internal dimensions 25cm x 21mm). The eluent was acetonitrile:water (2:1 v/v), which was removed under reduced pressure to afford the pure compounds.